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VARIATIONS IN THE BASOPHILIA OF NERVE CELLS ASSOCIATED WITH INCREASED CELL ACTIVITY AND FUNCTIONAL STRESS

BY

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All the large and medium types of nerve cell as well as some small, e.g., the small pyramidal cells of the cerebral cortex, possess a high degree of cytoplasmic basophilia, while in other small nerve cells, e.g., the small granule cells of the cerebellum and cerebrum, the basophilia is more or less confined to the nucleus (Einarson, 1945).

The high degree of cytoplasmic basophilia is due to the Nissl substance, the structural pattern of which differs in the various cell types. The Nissl substance contains at least three different components: nucleoprotein, acid and basic proteins. The first of these, the ribonucleic acid compound, is formed primarily round the nucleolus inside the nucleus, migrates towards the periphery of the nucleus, and then diffuses gradually through the nuclear membrane, close to which the cytoplasmic Nissl substance is formed (Einarson, 1932, 1933, 1934, 1935; Landström, Caspersson, and Wohlfart, 1941; Hydén, 1943). With basic dyes the nucleus and Nissl substance in normal resting nerve cells of any one particular type show a fairly constant structural picture (Einarson, 1935). Within each cell type, however, this picture exhibits marked changes, with variations in the functional or pathological activity of the cell. The most conspicuous of these changes are alterations in the quantity, affinity for basic dyes, and distribution of the Nissl substance, as well as alterations in the size and staining capacity of the nucleus, nucleolus, and nuclear membrane (Einarson, 1933, 1937; Hydén, 1943). There are also spontaneous variations in the affinity for dyes of the nerve cells in the central nervous systems of normal animals and man. But such changes are greatly enhanced by experimental procedures or by disease, which may increase neuronal activity (patho-functional stress), or may decrease or abolish it (patho-functional suppression).

In studying the different depths of staining, as may be seen in preparations stained with gallocyanin-chromalum, Einarson (1933, 1937, 1945) distinguished certain cell pictures.

Cell Conditions Visible after Gallocyanin-chromalum Staining

Hyperchromatic or Moderately Chromophilic Cells.—The cells are deeply stained. The dark, well-defined Nissl bodies make a comparatively sharp contrast against the interstitial, non-basophilic part of the cytoplasm, and several Nissl bodies are usually close to the nucleus. The nucleolus is intensely stained and often somewhat enlarged, and a relatively large number of stained particles is present in the nucleus.

Moderately Chromophobic Cells.—These show a decrease in the number and staining reaction of the Nissl bodies, and an increase in the nuclear chromatin. The nuclear membrane is intensely stained and the nucleolus enlarged. Perinuclear accumulations and nuclear caps of Nissl substance can be seen (peripheral chromophobia), but sometimes the Nissl substance is accumulated in the periphery of the cytoplasm (central chromophobia).

Extremely Chromophobic Cells.—The cells are pale and there is little or no staining substance. Both the nucleus and cytoplasm are shadow-like, and frequently the nucleus is eccentric in the cell body, which may be swollen, the picture perhaps resembling that of chromatolysis. The contours of the nucleus often appear irregular or shrivelled, and the dark, enlarged nucleolus may finally lose its capacity to stain inside the pale nucleus.

Extremely Chromophilic Cells.—These cells are intensely stained, with closely packed, dark Nissl bodies, while the interstitial non-basophilic substance of the cytoplasm is markedly reduced; sometimes the cells appear as dark, compactly stained bodies. The cell contours are well defined, and the dendrites

are often stained for a considerable distance. The nucleus is intensely stained, but the nucleolus is usually visible, despite the dark colour of the nucleus, whereas the nuclear membrane is hardly discernible (see also Einarson and Ringsted, 1938 ; Einarson and Lorentzen, 1946 ; Krogh, 1950 ; Lorentzen, 1950 ; Hartelius, 1952).

Chromoneutral Cells.—These cells represent the " normal " cell picture, showing the usual average staining capacity.

As to the functional meaning of these cell pictures, i.e., their significance as histological correlates of cellular activity, our investigations since 1932 on the staining reactions of nerve cells under various experimental conditions as well as our observations from human material have led to the following definitions :—

The chromoneutral condition represents cells at rest or in the usual state of normal activity (the indifferent phase of activity) ; moderate chromophilia (hyperchromasia) characterizes cells when their activity begins to increase (chromophilia of initial activity) ; moderate chromophobia gradually becoming more marked characterizes cells in increasing activity of longer duration (chromophobia of prolonged activity), while extreme chromophobia represents cells in a state of severe functional stress, fatigue, and exhaustion (chromophobia of fatigue and exhaustion). Extreme chromophilia characterizes cells either in a state of primary, active inhibition of prolonged duration (chromophilia of inhibition), or whose activity has been abolished for some time (chromophilia of suppressed activity) (Einarson, 1945, 1949, 1952 ; Krogh, 1950 ; Lorentzen, 1950). In pathological conditions extreme chromophobia may proceed to total dissolution of the cell, and extreme chromophilia will gradually proceed to cell sclerosis, irreparable cell atrophy, and cell shadows, or even to disappearance of the cell.

The purpose of this paper is to present additional evidence in support of the above definitions, particularly concerning the occurrence of chromophobia in cases of functional stress as well as in animal experiments.

The Staining Method

In the tissues of mammals, and at any rate in some lower animal species too, the essential part of the gallocyanin-chromalum staining consists in a selective binding of the dye-lake cations to the phosphoric acid groups of the polynucleotides, i.e., a salt of the lake-cations and the nucleic acids of the cell structures is formed. The staining progresses rapidly and completely withstands alcoholic dehydration and clearing in xylol. There is no further binding of the stain to the basophilic cell structures, even if the tissue remains in the staining solution longer than is necessary.

At the lower levels of *p*H, between *p*H 0·83 and 1·64, the staining is almost entirely caused by a binding of the dye to the nucleic acids of the cell structures ; there is, however, a non-specific staining (co-staining) of the tissue, independent of the presence of nucleic acids. From approximately *p*H 1·75 to 1·80 the co-staining increases, and it reaches a maximum between *p*H 3·3 and 3·5, falling abruptly from *p*H 3·75 to 4·07, due partly to an adsorption of the dye, i.e., lake-sulphate, in excess of the specific cation exchange, and partly to a binding of the lake-cations to the proteins of the cell structures, e.g., the Nissl substance. The latter will not occur on the acid side of the isoelectric point of the proteins. From *p*H 0·83 to 1·64 staining of structures other than the nucleic acids is very slight, as in this range no binding to the proteins will take place and the unspecific adsorption is reduced to a minimum. Although negligible at these low *p*H values, and practically insignificant in quantitative measurements, the unspecific adsorption nevertheless withstands the usual differentiating media. In quantitative estimates of the nucleic acids of the cell structures the error due to the persistent adsorption is amply compensated for by the progressive properties of the staining, which makes it particularly suitable for photometric estimation of the degree of cellular basophilia, and, as shown by this staining, the basophilia is essentially equal to the contents of nucleic acids. In fact, the specific part of the staining is in itself a quantitative-stoicheiometrical reaction for nucleic acids.

It is important to use only a suitable brand of gallocyanin,* and the purest obtainable chromalum. If these conditions, including a suitably low *p*H value, round 1·0, are fulfilled, the deep blue staining of the nucleic acids will show the highest degree of specificity, contrast, and stability, and the staining intensity is homogeneous throughout the tissue section. In these conditions, and taking into account the progressive nature of the staining as well as the error caused by the very slight unspecific adsorption, we think it justifiable to state that gallocyanin-chromalum is a specific stain for nucleic acids as these appear in the tissues of mammals and some lower animal species, fully acceptable for quantitative histological work. (For the theory and practice of gallocyanin-chromalum staining we refer especially to the paper by Einarson (1951) as well as to Pearse's (1953) book on histochemistry.)

The Occurrence of Chromophobia

The essential earlier investigations of the changes in structure and affinity for specific stains of the nerve cells following variations in the functional activity of the cells, in disease as well as in animal experiments, have been made by Einarson (1933, 1937, 1945), Einarson and Lorentzen (1946), Krogh (1945, 1950), Lorentzen (1950), Hartelius

* Satisfactory gallocyanin can be obtained from Hollborn and Söhne, Grübler and Co., National Aniline Division, 40 Rector Street, New York. Chromalum may be obtained from Hopkin and Williams Ltd., St. Cross Street, London, E.C.1.

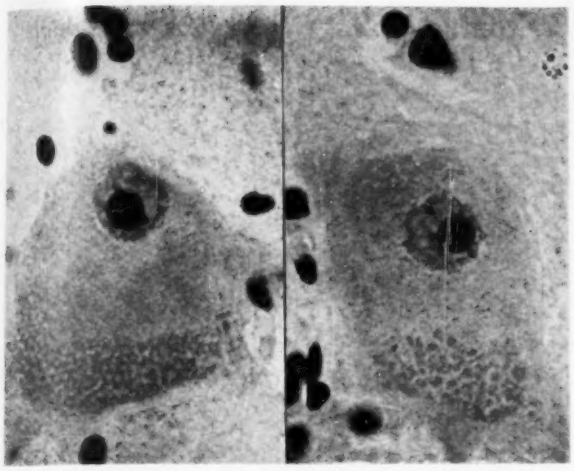

FIG. 1.—Acute delirium. Giant pyramidal cells of Betz. Extreme chromophobia. Gallocyanin-chromalum. × 600.

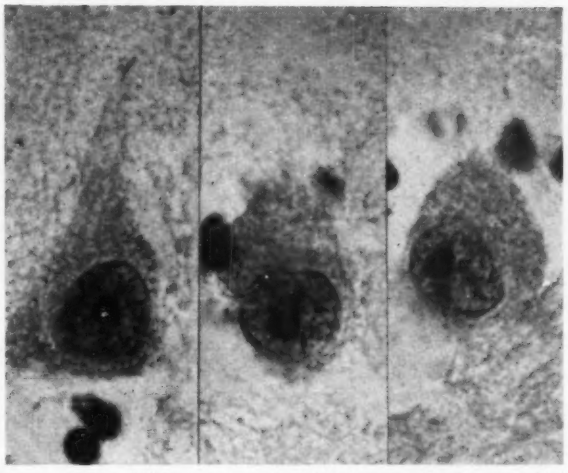

FIG. 2.—Acute delirium. Area 8 of Brodmann. Small pyramidal cells. Marked chromophobia. Gallocyanin-chromalum. × 800.

(1952), and others. The theoretical and technical aspects of the problem in general will not be considered in this paper.

Illustrative Case Reports

Acute Delirium (State Mental Hospital, Viborg, No. 10438 ; brain examination No. 241).—A woman aged 38 had a brother who had three times been admitted to a mental hospital but otherwise had no known familial disposition. The patient herself had always been mentally normal and sociable. Appendicectomy and tonsillectomy were performed in June and July, 1943. On August 15, 1947, the patient fell from her bicycle on to her head ; there was no apparent sign of cerebral concussion, but she sustained a fracture of the left radius, and was admitted to the surgical wards at Herning hospital. Five days later she suddenly became psychotic, and was admitted to the mental hospital. She was very anxious with explosive outbursts of excitement, shouting and screaming, gesticulating violently, and strongly hallucinated. She had to be restrained by a belt. After morphine-scopolamine and hypnophen she gradually calmed down, and next morning she was completely clear mentally and able to remember what had happened the evening before. Four days later, however, she became psychotic again, and on August 27, 1947, she died in exhaustion and hyperpyrexia after the utmost psychomotor exaltation, violence, and complete confusion. Laboratory examinations of the blood, spinal fluid, and urine showed nothing abnormal.

Necropsy showed nothing of particular interest in the internal organs, and there was no arteriosclerosis. Examination of the brain revealed a marked hyperaemia and oedema of the meninges as well as of the brain tissue itself. No sign of inflammation was seen anywhere, and, although congested, the blood vessels were normal everywhere ; in particular, there was no sign of arteriosclerosis of the brain vessels. There were no focal changes anywhere, except a few small haemorrhages by diapedesis in the medial nuclei of the thalamus. However, in every region of the cerebral cortex examined most of the nerve cells showed the typical picture of extreme chromophobia.

The findings in the present case serve to illustrate the chromophobic cell change as it appears in the cerebral cortex. Although the chromophobia is most pronounced in the large and medium pyramidal cells (Fig. 1), it is in the main quite conspicuous in the small pyramidal cells as well (Fig. 2). In the cells showing the most marked condition of extreme chromophobia the cytoplasm is very swollen, and there is almost no nucleoprotein left. The nucleolus is very large and darkly stained, and the nuclear contours become more or less shrivelled (Fig. 1). In our opinion and experience over many years, the interpretation must be that the power of the cell to regenerate nucleoproteins is being exhausted, as the formation of cytoplasmic nucleic acid could not possibly keep pace with the increased consumption due to the abnormal rise in functional demands on the neuron.

The chromophobic cell change is widespread in this brain. As well as in the cerebral cortex, a more or less pronounced chromophobia, in many places reaching an extreme degree, is to be seen practically everywhere ; e.g., in the thalamus, hypothalamus, brain-stem, and in the Purkinje cells and dentate nucleus of the cerebellum. Numerous nerve cells show a moderate amount of chromolipoid in the cytoplasm.

Acute Delirium (State Mental Hospital, Nykøbing Sjælland, No. 11107 ; brain examination No. 723).—A man aged 68 was admitted to hospital on July 24, 1951. No familial disposition was known. Six years before he had been treated for prostatic hypertrophy. He had never had any head injury. The patient had always been mentally normal and sociable although of a rather

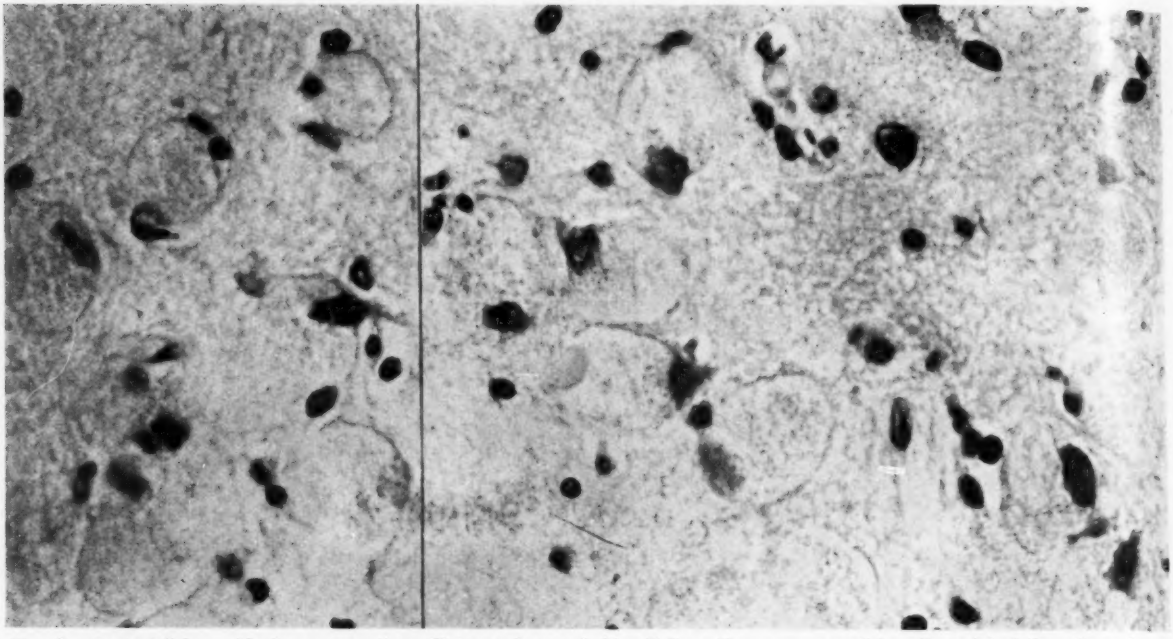

FIG. 3.—Acute delirium. Nucleus supraopticus. Extreme chromophobia. Balloon-like appearance of the cells, and depletion of cytoplasmic nucleic acid. Gallocyanin-chromalum. × 500.

reserved temperament. During the last two years he had become increasingly forgetful, apathetic, and taciturn. The last two months before his mental illness he had been somewhat restless, and the last eight days before the admission he had been agitated, in high spirits, talking very much, and somewhat confused, showing a quite unusual, strange behaviour with marked emotional instability. On admission he was very agitated and reluctant, anxious, and slightly confused, with outbursts of excitement and violence, and had to be controlled in a belt ; he was unable to give any relevant information. He looked older than his age ; there was considerable peripheral arteriosclerosis, with marked arcus senilis and a central paresis of the left face. Next day there were marked anxiety and restlessness, and confusion with hallucinations developed. During the following days he was very excited, constantly talking, shouting, screaming, and gesticulating violently, and on July 30, 1951, he died in exhaustion and hyperpyrexia.

The spinal fluid showed normal values for albumin, globulin, and cells, and Pandy's test was negative ; the Wassermann test was negative in the blood and spinal fluid ; the sedimentation test was 8 mm. in one hour ; serum bicarbonate and chloride levels were normal ; total serum cholesterol was 138 mg. per 100 ml.

Necropsy showed hyperaemia of the brain, stasis and oedema of the lungs, atherosclerosis of the aorta and coronary arteries, several small adenomata in the cortex of the adrenals, hyperplasia of the spleen, and hyperaemia and parenchymatous degeneration of the kidneys with intracanalicular calculi of the renal medulla.

Neuropathological examination revealed considerable oedema of the brain and meninges, and only moderate arteriosclerosis of the blood vessels at the base of the brain. No focal changes or haemorrhages were seen anywhere. The brain weighed 1,480 g.

Microscopically there is marked dilatation and congestion of veins and capillaries, and the smaller arteries and arterioles show only moderate sclerotic changes. Some atheromatous plaques are seen in only a few larger arteries of the corpus striatum. Round the ventricles the oedematous brain tissue contains numerous amyloid bodies, and in the cortex of the frontal lobes as well as in the hippocampus a few senile plaques may be seen. Many of the nerve cells, particularly in the cerebral cortex, contain a considerable amount of chromolipoid in the cytoplasm.

The most outstanding and characteristic finding, however, is the pronounced and widespread extreme degree of chromophobia of the nerve cells. This occurs practically everywhere in the brain, together with many more moderately chromophobic cells. Although in the cerebral cortex the chromophobic cell picture is not quite so pronounced as in the previous case it is nevertheless very conspicuous both in the larger and smaller pyramidal cells. The same is true of the thalamus, hypothalamus, and brain-stem. In all these parts of the brain the great majority of the nerve cells show moderate to extreme chromophobia. Chromophobia is very pronounced and characteristic in the hypothalamus.

Although the pathological significance of chromo-

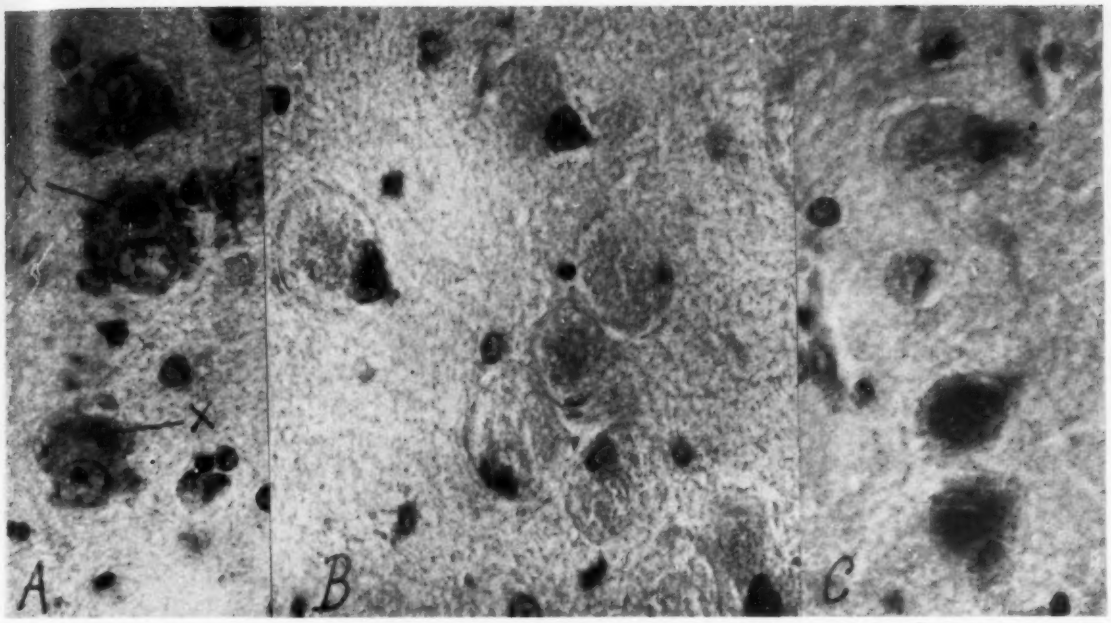

FIG. 4.—Acute delirium. Nucleus supraopticus. × 500. (A) Moderate chromophobia; cytoplasmic inclusions (x) stained with toluidine blue at *p*H 3·9. (B) Extreme chromophobia; diffuse cytoplasmic staining with toluidine blue at *p*H 3·9. (C) Extreme chromophobia; marked diffuse cytoplasmic staining with toluidine blue at *p*H 4·4. The toluidine blue stainings of the cytoplasm are superimposed on gallocyanin-chromalum.

phobia, especially its moderate stages, is difficult to estimate in the nerve cells of the hypothalamus on account of the special character of the cells, it is generally quite conspicuous. Chromophobia ranges in degree from moderate to extreme, and is widely distributed in the hypothalamic nuclei, e.g., in the supraoptic, paraventricular, medial and lateral tuberal, and posterior hypothalamic nuclei. It is most intense in the cells of the supraoptic nucleus (Figs. 3 to 5), and, on account of the structural peculiarities of these unusual nerve cells, only the extreme state of chromophobia will be emphasized.

Most of the cells of the supraoptic nucleus are extremely swollen, of an almost balloon-like appearance, with a shrunken, eccentrically displaced nucleus, and the cytoplasm is left unstained by gallocyanin-chromalum; it is really depleted of nucleic acid. In some of the cells the nucleus is still hyperchromatic, in others it has almost lost its staining capacity, and appears as a shadow (Fig. 3). When stained with toluidine blue according to Einarson (1945) there is no staining of the cytoplasm at *p*H values on the acid side of the isoelectric point of the Nissl substance. At *p*H 3·9 staining of the cytoplasm with toluidine blue becomes visible. In the more moderately chromophobic cells this appears as distinct cytoplasmic inclusions (Fig. 4A) while in the extremely chromophobic cells it appears as a faint diffuse staining (Fig. 4B) to become quite conspicuous at *p*H 4·4 (Fig. 4C). In our opinion staining with toluidine blue is probably due to the presence of some cytoplasmic protein substance. For comparison, Fig. 5 shows the extremely chromophobic cells as they appear in preparations stained by Bodian's method. In the paraventricular nucleus

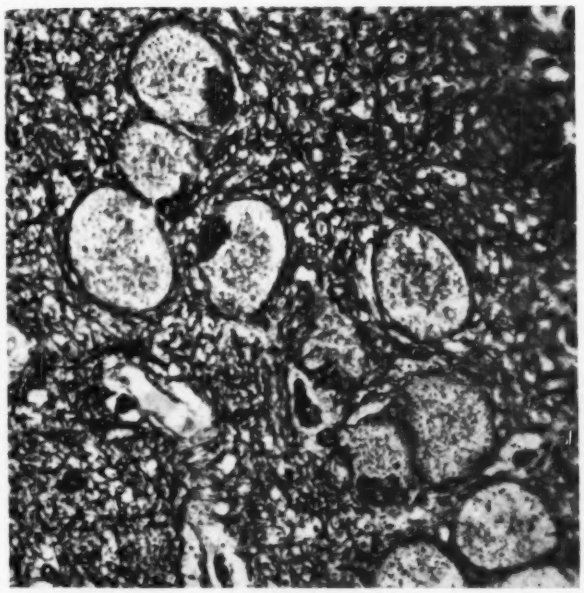

FIG. 5.—Acute delirium. Nucleus supraopticus. Extreme chromophobia. Balloon-like swelling of the cells. Bodian's stain. × 500.

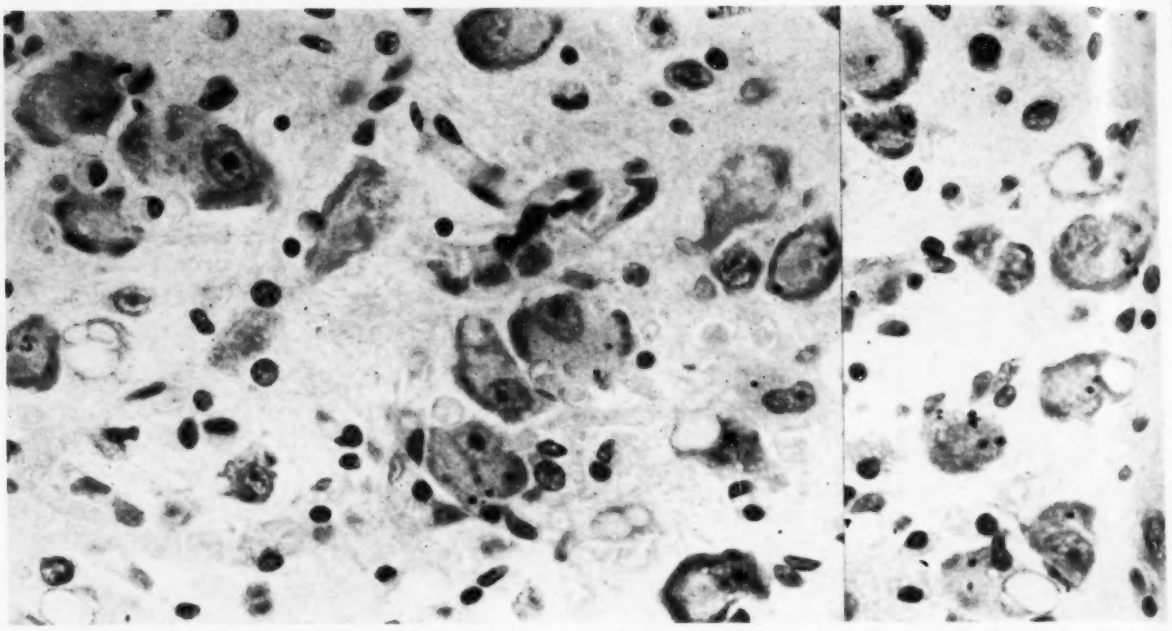

FIG. 6.—Acute delirium. Nucleus paraventricularis. Marked chromophobia. Vacuoles and dark granular inclusions in the cytoplasm. Gallocyanin-chromalum. × 500.

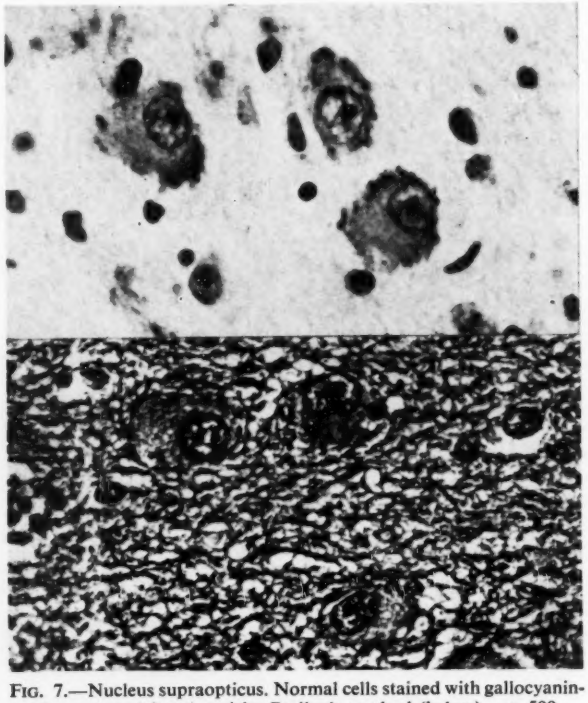

FIG. 7.—Nucleus supraopticus. Normal cells stained with gallocyanin-chromalum (above) and by Bodian's method (below). × 500.

most of the cells present an appearance of more moderate stages of chromophobia (Fig. 6), but many of them contain big vacuoles and some dark granular inclusions in their cytoplasm.

In comprehensive surveys Greving (1928), Le Gros Clark, Beattie, Riddoch, and Dott (1938), and Scharrer and Scharrer (1940, 1954) discuss the normal cytology of the hypothalamic nuclei and the neurosecretory activity of the cells. Here it is sufficient to say that the supraoptic and paraventricular nuclei vary widely in structure, particularly in the cytoplasmic content of vacuoles, colloid droplets, and granules of various kinds, and in the mutual relation of these inclusions to the Nissl bodies and the nucleus. It is especially important to note that in these unusual nerve cells the nuclei generally take eccentric positions, the nuclear membranes are often distinctly stained, sometimes with perinuclear deposits of basophilic substance, and the coarse Nissl bodies occupy the periphery of the cell body, of which the interior shows a reduced, diffuse, or dust-like staining of the cytoplasm (Fig. 7). Thus, the normal cell pictures resemble those of moderate chromatolysis or chromophobia, although the pseudo-pathological appearance of the cells has repeatedly been pointed out by several authors. In fact, no precise line of demarcation can be drawn between the normal variations of basophilia and abnormal chromophobia, i.e., we are dealing with gradual transitions of basic staining affinity. In other words, it is difficult to tell where chromophobia of normal activity ends and that of abnormal hyperactivity begins in the cells of the hypothalamic nuclei. Thus, the significance of the more moderate stages of chromophobia remains

questionable in this particular region while sufficient data based on the gallocyanin-chromalum staining are not available. Possibly such data might reveal a significant difference between the normal and the findings in cases of acute, lethal psychoses. In fact, studies of a larger series carried out by Bom in 1954 and not yet published seem to indicate that this actually is the case. In two preliminary reports Bom (1946, 1953) pointed out the pronounced increase of the cellular vacuolization in the hypothalamus frequently met with in acute lethal psychoses as well as the marked chromophobia. So far Bom is the only other investigator who has used gallocyanin-chromalum staining in studies of this kind. Undoubtedly, however, the cell pictures of extreme chromophobia (Figs. 3 to 5) are pathologically significant as real cytological correlates of the abnormal functional stress on the neurons, and typical transitional stages of chromophobia can be seen within the same hypothalamic nucleus.

In the present paper the cell pictures of chromophobia observed in the hypothalamus have been estimated only in regard to their significance as changes following neuronal activity, intimately connected with a loss of nucleic acid from the cytoplasm, but no attempt has been made to correlate the findings with the cytological criteria of neurosecretory activity ; and the hypophysis was not at our disposal.

Deaths from Convulsant Therapy with Metrazol and Insulin.—We have examined the brains from a few psychotic patients who have died as a result of convulsant drug therapy, either during or shortly after the artificially induced shocks. One patient developed spontaneous epileptic seizures following the shock therapy, and died as a result.

The changes of the nerve cells in cases of death from metrazol shock have been briefly reported and illustrated by Einarson and Lorentzen (1946) and by Krogh and Einarson (1954), and the cell changes in cases of death from insulin shock have been studied by Lorentzen (1954; still unpublished). It is sufficient to note here that the cell picture of chromophobia, ranging from moderate to extreme degrees, is a most conspicuous and widely distributed feature in the cerebral cortex and the brain-stem. In the motor areas of the cortex it has reached its most advanced stages, affecting the great majority of the cells in all the cortical layers. The giant pyramidal cells of Betz are extremely swollen, with a more or less shrivelled and eccentrically displaced nucleus, and their cytoplasm is ghost-like, with practically no remnants of nucleic acid left. In some of the cells the large nucleolus is still darkly stained ; in others it has become quite pale. The cell picture is fundamentally the same as shown in Figs. 1 and 2.

Traumatic Encephalopathy and Symptomatic Epilepsy (State Mental Hospital, Aarhus, No. 18790 ; brain examination No. 272).—A woman aged 25 had no known familial history of mental disorder, but an aunt has been a patient in the Viborg Mental Hospital for 10 years. When 5 years old, while playing, the patient was hit hard on the right temple with a wooden shoe ; however, there was no loss of consciousness and no nausea or vomiting. At the age of 7 she was run down by a motor-cycle, an accident that involved cerebral concussion. From her sixth year she has had periods of unconsciousness and epileptic attacks. From 1930 to 1937 she was a patient at Moltke's Infirmary and there had numerous Jacksonian epileptic attacks with myoclonus in the left arm, platysma, and left side of the face. A light paresis of the left orbicularis oculi muscle and left arm, reduced sensibility on the left side of the body (face, neck, shoulder, arm), and light parageusia developed.

From 1937 to 1941 she stayed at Filadelfia, the Danish hospital for epileptics, and from there she was twice (July, 1940, and January, 1941) transferred to the Department of Neurosurgery, National Hospital, Copenhagen, for examination for a possible cortical encephalitis, an atrophic brain affection (traumatic ?), or a vascular malformation, causing partial epilepsy. On January 17, 1941, she had numerous epileptic fits with loss of consciousness, opisthotonos, and involuntary urination, and gradually there developed status epilepticus, from which she was finally relieved by narcosis. During the following two days she had nine epileptic fits, between each of which she was completely awake and talked rationally ; each fit lasted three to 10 minutes. On January 20, 1941, she was operated on, the central part of the right cerebral hemisphere being exposed. The cortex looked congested with arachnoidal adhesions in the Sylvian fissure. About 10 cm. from the median line there was a small, atrophic portion of cortex in the precentral sulcus, with a deep-set, spiral vein. The vein with the surrounding tissue was coagulated, and a piece of arachnoid was removed (Prof. Busch). Subsequent microscopical examination showed a thickened arachnoid with vascular growth into it ; the dura was normal (Dr. Christensen). On February 10 the patient was transferred to Filadelfia, and stayed there until December 15, 1941, when she left for her home.

In the following years she was repeatedly admitted to various hospital departments, including the Aarhus State Mental Hospital, on account of epilepsy and several suicidal attempts, and on July 7, 1947, she was for the third time admitted to the Aarhus State Mental Hospital. In hospital her condition varied from normal behaviour to an intense verbal and motor restlessness, and she had numerous epileptic attacks. After an epileptic seizure during the night between September 15 and 16, she slept quietly, and died in her bed early in the morning of September 16, 1947, without further convulsions or any premonitory symptoms. Laboratory examinations

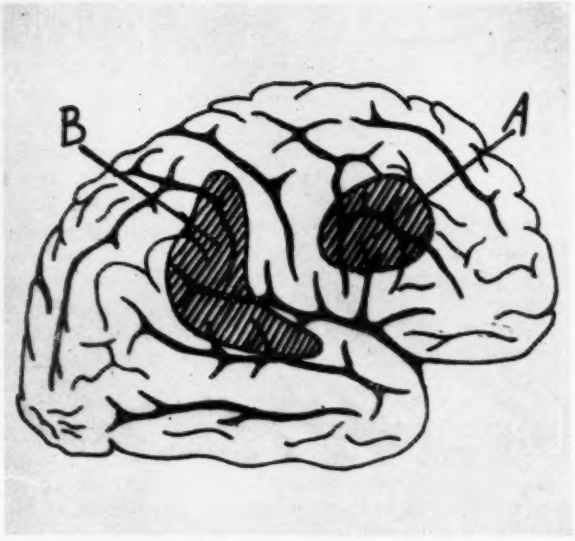

FIG. 8.—Traumatic epilepsy. Diagram indicating the approximate sites (the lined areas A and B) of meningeal adhesions and the most marked glial changes.

showed nothing abnormal, either in the blood, spinal fluid, or urine. The temperature was always normal.

Necropsy showed stasis and oedema of the lungs, ecchymoses of the pericardium, and acute stasis of the abdominal organs. No arteriosclerosis was seen anywhere.

FIG. 9.—Traumatic epilepsy. Middle frontal gyrus. Very pronounced hyperplasia of the astrocytes in the subcortical white matter and the deepest layers of the cortex. Bodian's stain. × 95.

On examination of the brain there were meningeal adhesions to the cortex of the right hemisphere in two places : first, to a slightly depressed area round the inferior frontal sulcus, extending a little backwards into the anterior central gyrus (A, Fig. 8); secondly, to an area comprising the hind part of the superior temporal gyrus and the opercular parts of the parietal lobe, extending upwards into the postcentral gyrus (B, Fig. 8). In both these areas and the adjacent parts of the cortex there is a considerable glial proliferation, with hyperplasia of the small astrocytes, and some increase in glial fibres, distributed in the most superficial cortical layer and just beneath the pia. In the subcortical white matter and the deepest layer of the cortex, particularly in area A (Fig. 8) and its adjacent parts, there is, however, a most pronounced proliferation and hyperplasia of the large astrocytes, many of which are extremely

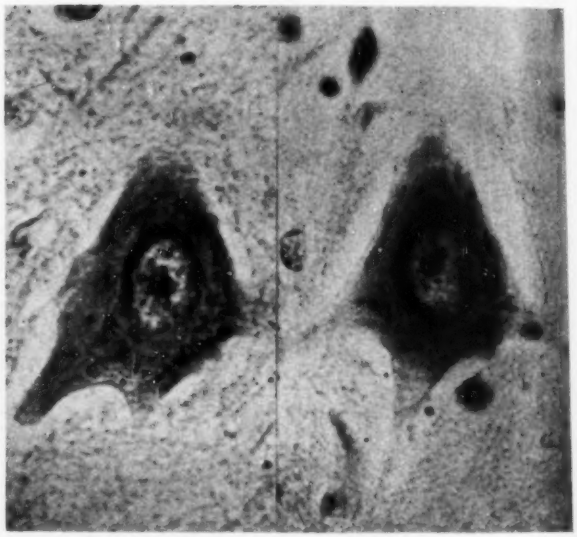

FIG. 10.—Traumatic epilepsy. Area 4 of Brodmann. Giant pyramidal cells. Marked perinuclear deposition of basophilic substance (nucleic acid). Gallocyanin-chromalum. × 600.

swollen (Fig. 9). For the rest, the meninges are oedematous, and the meningeal blood vessels are dilated and congested, but there is no actual sign of inflammation anywhere. The vessel walls are normal both in the meninges and the brain tissue itself. In several places the perivascular spaces are dilated on account of the oedema.

In our opinion there can be no doubt that the glial changes developed in connexion with a traumatic lesion which also provoked post-traumatic epilepsy, although its incidence in closed head injuries is comparatively low (Russell, 1951 ; Russell and Whitty, 1952 ; Bertrand and Harriman, 1953).

In this case the cell pictures are interesting, particularly in the cerebral cortex. Generally, chromophobia is the most outstanding feature not only in the cortex but in the thalamus and brain-stem as well. It is most prominent in the cortex of the frontal lobes, where the vast majority of the pyramidal cells show it in various stages. The characteristic distribution of the stainable substance (nucleic acid) in the cell body and its structural relation to the unstained part of the

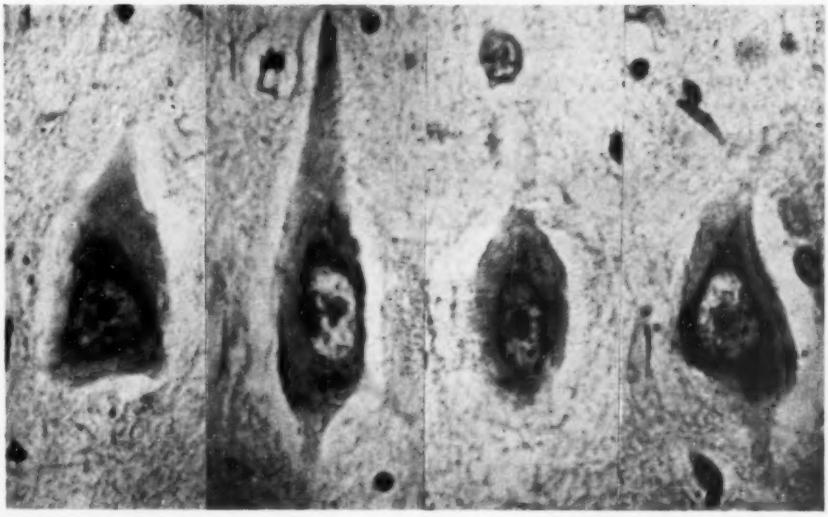

FIG. 12.—Traumatic epilepsy. Area 6 of Brodmann. Middle-sized pyramidal cells with perinuclear accumulations and nuclear caps of basophilic substance. Gallocyanin-chromalum. × 600.

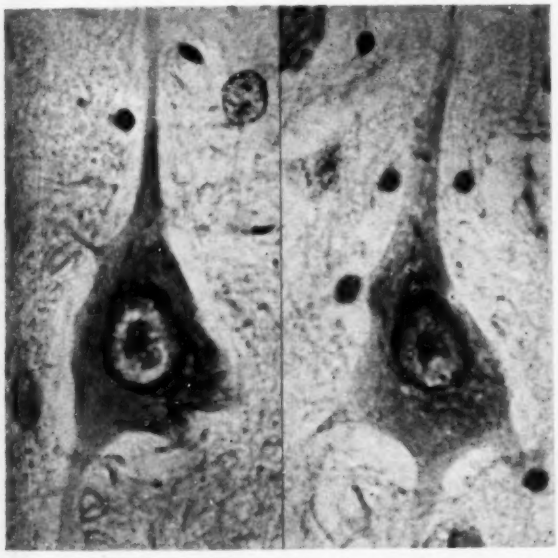

FIG. 11.—Traumatic epilepsy. Area 44 of Brodmann. Large pyramidal cells showing marked deposition of nucleic acid round the nucleus (peripheral chromophobia). Gallocyanin-chromalum. × 600.

cytoplasm are especially to be emphasized (Figs. 10 to 13). Thus, the cell picture of moderate chromophobia, with an accumulation of deeply stained substance (nucleic acid) round the nucleus, surrounded by a relatively broad peripheral zone of non-basophilic, very light or indifferently stained cytoplasm is a prominent feature. The cells are but slightly swollen, and their pyramidal form is mostly well preserved (Figs. 10 to 13). This picture resembles the so-called " peripheral chromatolysis ", but for several reasons we prefer to call it " peripheral chromophobia ". In some of the largest pyramidal cells, especially the giant cells of Betz (Fig. 13), the cytoplasm is also vacuolized.

The cell picture described is especially conspicuous in the large and medium-sized pyramidal cells, most characteristically in the areas 4, 6, 8, 44, 45, and 46 of Brodmann. In every area examined, however,

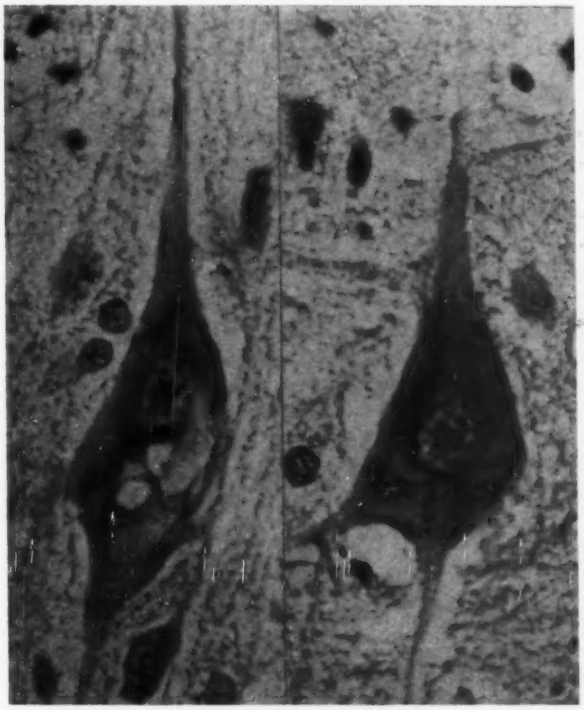

FIG. 13.—Traumatic epilepsy. Giant pyramidal cells of Betz showing perinuclear distribution of basophilic substance and vacuolization of the cytoplasm. Gallocyanin-chromalum. × 600.

some moderately chromophobic cells showing an accumulation of basophilic substance in the periphery of the cytoplasm with a light inner or perinuclear zone may be seen (" central chromophobia "), and still other cells show both peripheral and perinuclear accumulations of basophilic substance, with a light intermediary zone. In fact, we are dealing with transitional cell pictures of moderate chromophobia, but whichever the pattern observed the nuclear membrane is always strongly basophilic. Some markedly swollen cells, resembling extreme chromophobia, may also be seen.

Our interpretation of the appearances in Figs.10 to 13 is that the cells are in a state of restoration from a more advanced stage of chromophobia, i.e., of the regeneration of the Nissl substance after the abnormal neuronal discharge which constitutes the epileptic fit. In fact, the sections indicate very clearly how cytoplasmic nucleic acid is deposited round the nucleus, making the nuclear membrane strongly basophilic. This observation provides convincing evidence in support of the theory that the nucleic acid component of the cytoplasm is formed primarily round the nucleolus inside the nucleus, migrates towards the periphery of the nucleus, and then diffuses through the nuclear membrane into the cytoplasm where it is incorporated as a constituent of the basophilic elements (Einarson, 1933, 1935). Thus, we are dealing with the structural picture of a certain phase of material interchange between nucleus and cytoplasm.

Animal Experiments

Our experimental material is derived from the usual experimental animals (rats, rabbits, cats, dogs), but similar structural effects of neuronal hyperactivity can be shown in molluscs, and in this paper we are especially concerned with the latter.

Stimulation of the Ganglia of *Aplysia* (Sea Hare).—The specimens of this big marine snail used in our experiments weighed about 500 g. The greater part of the nervous system of *Aplysia* consists of a ring of ganglia situated around the oesophagus. The nerve cells of these ganglia are very large, ranging from 150 to 400 microns in diameter. The nuclei vary with the size of the cells, and may reach a maximum of about 250 microns. The ganglion cells were subjected to electric stimulation, and stained with gallocyanin-chromalum.

A wire of stainless steel enclosed in a small glass tube was inserted through the mouth of the animal and fixed there in such a way that the point of the wire protruding from the glass tube was exactly at a level with the ganglia. The animal was placed in a small aquarium in which the water was renewed every 10 seconds by a constant flow of fresh oxygenated sea water. The second electrode was a plate of stainless steel placed at the bottom of the aquarium. The stimulator used was the Harvard induction coil.

During stimulation the animal responded with a very strong tetanic contraction of all muscles, to such an extent that the animal almost resembled a ball. After a stimulation period of about one and a half to three hours the muscles relaxed, and stimulation was then discontinued and the animal killed. The ganglia were immediately removed and fixed in a saturated solution of picric acid in sea water and

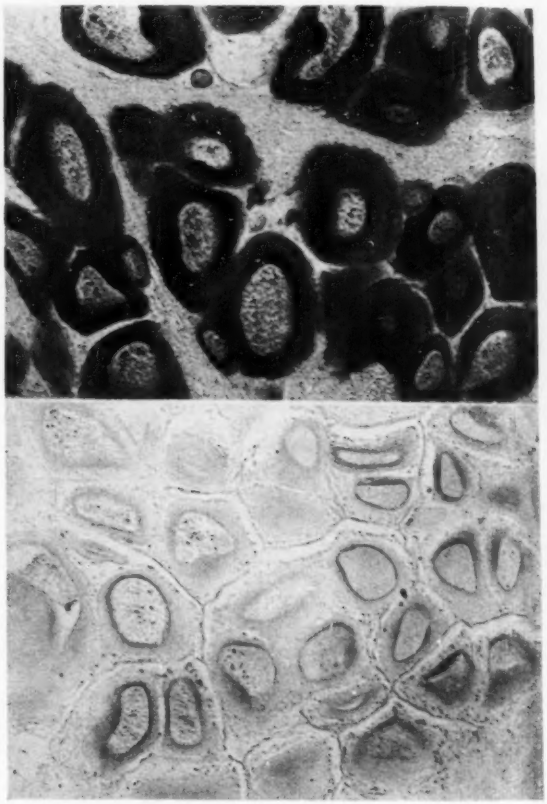

FIG. 14.—Ganglion cells of *Aplysia*. Normal cells (above) showing considerable cytoplasmic basophilia. After stimulation for two hours the cells (below) show a very pronounced chromophobia. Gallocyanin-chromalum. × 100.

embedded in paraffin. Ganglia from stimulated animals and from normal control animals were embedded in the same block and cut together at a thickness of 10 microns.

The histological findings were very uniform. In all the stimulated animals the nerve cells were almost empty of cytoplasmic nucleic acid, as compared with the normal control animals in which the nerve cells contained a considerable amount of nucleic acid in

the cytoplasm (Fig. 14). After gallocyanin-chromalum staining this is indicated by the difference in the affinity for staining of the nerve cells of the normal and the stimulated animals respectively.

In the cells of the normal group there is marked cytoplasmic basophilia, while those of the stimulated group show a highly reduced basophilia, i.e., there is pronounced chromophobia of the cells (Fig. 14). (The sections were photographed on the same film and produced under exactly the same conditions.)

Within each group of ganglia, i.e., the normal and the stimulated, the cells show certain mutual variations in their degree of basophilia. Moreover, the basophilia varies at different spots in the cytoplasm of the same cell, but the difference between the average degrees of basophilia of the normal and stimulated groups is always very clear.

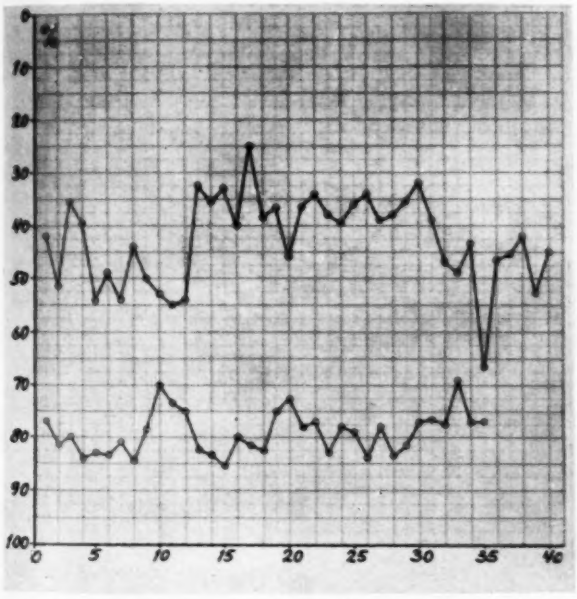

FIG. 15.—Graph showing the mean photometric values of 120 and 105 measurements respectively of the cytoplasmic basophilia in 40 normal (above) and 35 stimulated ganglion cells of *Aplysia* (below). Gallocyanin-chromalum ; *p*H 1·64.

In order to elucidate these observations, and to put them on a relative-quantitative basis, we subjected our material to microphotometric determinations of the basophilia by means of the technique used for many years in our laboratory and described by Einarson (1945). It should be mentioned that in the beginning we used the ocular photo-cell of Dr. B. Lange, Berlin, but now we are using the selenium photo-cell, type A, of Evans Electro-selenium Ltd., and a mirror galvanometer of Siemens Halske, Berlin, with a scale distance of 1·5 metres. The stabilizer used is the " Stavolt " of Struers Laboratory, Copenhagen. The maximum light absorption of the gallocyanin-chromalum solution is at approximately 560 mμ, as determined by the Beckman spectrophotometer ; this corresponds with the maximum relative sensitivity of the photo-cell used.

Fig. 15 illustrates our measurements in 40 normal and 35 stimulated cells from the same section. The number of cells is entered along the abscissa. The ordinate indicates the amount of light transmitted by the stained cytoplasm as a percentage of that transmitted by the slide, the layer of balsam, and the cover glass. Each point on the graph represents the mean value of three determinations at different spots in the same cell. Thus, the total of determinations in this particular section is 120 and 105 respectively. It is to be seen that the average light transmission by the normal cells (above) is about 42 to 43%, while that of the stimulated cells (below) is about 79 to 80%. This is a clear indication of the reduced basophilia of the stimulated cells.

Chronic Vitamin-E Deficiency.—Variations in the basophilia of nerve cells, including chromophobia, are particularly conspicuous in vitamin-E deficiency as produced in adult rats by Einarson and Ringsted (1938). Although somewhat variable, the changes of basophilia mostly pass through several consecutive structural stages. From the normal condition of chromoneutrality the nerve cells pass through stages of hyperchromasia and chromophobia followed by increasing basophilia leading to extreme chromophilia, and finally to irreparable cell atrophy, with a marked reduction or even loss of their affinity for staining. These cell changes may roughly be correlated with the clinical symptoms displayed by the rats during the progress of the deficiency disease from its outset to the end. The cell pictures are complicated by the occurrence of deposits of acid-fast, fluorescent products in the cytoplasm (Einarson, 1953, 1954). As these increase the nucleic acid disappears from the cytoplasm (cellular lipodystrophy). Thus, this metabolic derangement induces a secondary reduction in the basophilia of the nerve cells in addition to the primary changes.

Notwithstanding this complication we have subjected our material to renewed photometric determinations of the basophilia, and so far the results definitely tend to corroborate our concepts of the functional meaning of the cell pictures. These results will be reported in a separate paper.

Acute Hypoxia, Insulin Shock, and Electrically Induced Convulsions.—Studies of the variations in the basophilia of nerve cells in experimental acute

hypoxia (Krogh, 1945, 1950), in insulin shock (Lorentzen, 1950), and in electrically induced convulsions (Hartelius, 1952) were carried out by means of gallocyanin-chromalum staining.

In all three categories of experiments the nerve-cell changes showed a considerable variability, largely according to the varied experimental conditions. Generally, however, various stages of chromophobia were quite conspicuous, especially in Krogh's and Lorentzen's material (rabbits). In the material of Hartelius (cats) the nerve-cell changes noted were slight, but there was a statistically significant difference between the control animals and those subjected to electric convulsant treatment with regard to the variability of the cell changes, which were in the form of various stages of chromophobia, frequently with coincident nuclear hyperchromatism; the arrangement of the cells was mainly focal.

It is to be emphasized in particular that at the milder degrees of hypoxia which Krogh obtained by cutting off the blood flow to the lumbar part of the spinal cord (compression of the abdominal aorta) for shorter periods of time, e.g., 20 minutes, many of the animals developed spastic paralysis of the hind legs, and Krogh correlated the clinical pictures, electromyograms, and cell changes of the animals. The surviving anterior horn cells, which innervated the spastic muscles, invariably showed much lower contents of cytoplasmic nucleic acid than normal cells do, and they were very sensitive to proprioceptive impulses. By alternately stretching and bending the spastic hind legs for a long period the cells in question can be exhausted and made to show the picture of extreme chromophobia (Krogh and Einarson, 1954). These experiments indicate that the cell pictures of chromophobia are to be interpreted as structural correlates of increased and abnormal neuronal discharge.

Summary

After staining nerve cells with gallocyanin-chromalum, a quantitative and stoicheiometrical staining reaction for nucleic acids, the cell pictures exhibit marked changes with variations in the functional and pathological activity of the cells. These changes consist in variations in the basophilia of the cytoplasm, nucleus, nucleolus, and nuclear membrane, accompanied by alterations in the form of the cell body and nucleus, and size of the nucleolus, as well as characteristic changes in the distribution of the basophilic elements in the cytoplasm and displacement of the nucleus inside the cell body. The fundamental cell stages of basophilia (chromoneutrality, hyperchromasia, chromophobia, chromophilia) are described.

Spontaneous variations in the basic staining reaction of the nerve cells constantly occur in the central nervous systems of normal animals and man, but are greatly enhanced by experimental procedures or in disease.

Chromophobia in certain human cases of pathofunctional stress (acute delirium, death from convulsant treatment, traumatic epilepsy), as well as in the ganglion cells of *Aplysia* after electric stimulation, is described.

All the evidence indicates that the cell pictures of chromophobia are to be interpreted as structural correlates of increased activity and abnormal neuronal discharge. Certain characteristic cell pictures provide strong evidence in support of the theory (Einarson, 1933, 1935) that the nucleic acid of the cytoplasm is formed primarily round the nucleolus inside the nucleus and then diffuses through the nuclear membrane to become a constituent of the basophilic elements in the cytoplasm.

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ARGYROPHILE BODIES IN THE HUMAN SPINAL CORD

BY

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Certain argyrophile bodies have been found in the adult human spinal cord which do not seem to have been described before. These bodies occur mainly in the anterior horns of the lumbosacral region, and they have been found in every case of a large series of patients dying from a variety of conditions.

The purpose of this paper is to describe and illustrate these argyrophile bodies, to discuss their significance, and, especially, to consider whether they are artefacts or whether they are pathological or anatomical structures.

Material and Method

Over 80 spinal cords were examined. In 40, the patients had undergone the operation of antero-lateral chordotomy to relieve the pain of cancer not involving the central nervous system. The other cases had been collected at random from necropsy material in a general hospital to form a control group. In this group there had been no operation on the spinal cord ; these patients had the following conditions at the time of death : myasthenia gravis, peritonitis, Parkinson's disease, uraemia, alcoholism, pulmonary tuberculosis, and malignant disease ; one young man died as the result of an accident.

The argyrophile bodies which are to be described were found in all 80 cords examined ; that is to say they were present in all the control group as well as all the cords from patients who had had chordotomy.

All descriptions in this paper refer to every cord examined. The ages of the patients varied from 20 to 84 years, with the majority in the 50 to 70 year group. The length of the illness varied from a few hours to several years ; in one case (accident) there was no illness before death. The interval between death and necropsy varied from one hour to three days.

Sections were examined from all segments of each cord in the chordotomy series and from representative segments in the control series. In all cases celloidin sections, and in some cases paraffin sections also, were prepared. The staining methods used were haematoxylin and eosin, haematoxylin and van Gieson's method, thionin, Anderson's Victoria blue, Holzer's method, Mallory's phosphotungstic acid haematoxylin, Gros-Bielschowsky's silver impregnation, Loyez's myelin stain ; in adjacent blocks in most cases Weigert-Pal and Marchi preparations were also made.

Results

In every case, in the silver preparations of the lumbar and sacral segments numerous rounded argyrophile bodies are present (Figs. 1 and 2). The great majority of them are in a definite group lying in the anterior part of the anterior horn ; a very few are also scattered about the anterior and posterior horns in some cords. The anterior group in the lumbosacral cord lies close to the white matter, medial to the antero-lateral column of motor cells, in a region where there are few large neurons but many axons of motor cells. This site is shown in Figs. 1 and 2. The number of silver bodies in a transverse section varies from segment to segment and from case to case. They are present from the first lumbar to the third sacral segment ; the largest number of bodies usually occurs in the third or fourth lumbar and the second sacral segments, where there are from eight to 60 in a section, while there may be only four or five of them at the other levels. A very few are also present in a similar site in the lower cervical segments.

The bodies are rounded or pear-shaped, and in many a " stalk " can be seen at one pole. They lie among the axons. Whether they are attached to the axons or not could not be determined in longitudinal or transverse sections, for the dimensions of the bodies are such that it is difficult to obtain all parts of the body in one plane of section. It looks as though some are attached to the axons, but the majority appear to be free (see Figs. 3 to 5). The stalk itself is usually of lesser diameter than the large axons, but in some instances a thicker stalk is present. The bodies have the same appearance in transverse and longitudinal sections.

The greatest diameter of the bodies varies between 5 and 30 μ ; in the majority it measures 14 to 20 μ.

Allowing for the difference in sections after celloidin and paraffin embedding, the bodies have the same appearance in both preparations, and are

FIG. 1

similar after impregnation by the Gros-Bielschowsky or the Holmes method. No abnormality in any section stained by the other methods could be detected, other than those clearly associated with the chordotomy.

Discussion

Are Argyrophile Bodies Artefacts?—It is now necessary to consider whether these argyrophile bodies are artefacts, and, if so, what are the possible factors involved.

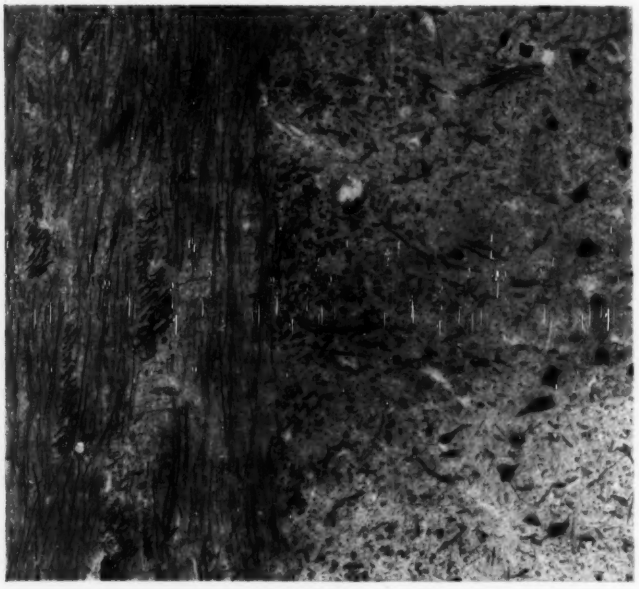

FIG. 2

Delay before Fixation.—The bodies were found in all the spinal cords examined. The interval between death and fixation of the cords varied from one hour to three days. This range would appear to eliminate the possibility of this interval being a factor in the production of the bodies. No correlation between the number of argyrophile bodies in a case and the duration between death and fixation could be established.

Trauma at Necropsy.—The bodies have the same staining reactions as axons. In view of this it would seem likely that, if they are the result of trauma, they represent damage to axons.

All the material, including the control group, is part of a planned investigation on the central nervous system, entailing the examination of the entire cord and brain for histological changes associated with the operation of chordotomy. For this reason care was taken at necropsy to avoid any trauma to the cord or nerve roots which might complicate interpretation of the histological appearances.

In some cases the cord was removed unfixed, and then fixed in 20% formol-saline. In others it was fixed *in situ* by the injection of 20% formol-saline into the cisterna magna, while cerebrospinal fluid was drained by lumbar puncture. The cord was removed 24 hours later. No more tension was exerted on the lumbosacral anterior nerve roots than on those of any other part of the cord, or on the cranial nerves. A very few argyrophile bodies were found in the cervical cord, but none in the cranial nerves or brain, even in association with nerves subjected

FIG. 1.—Low-power view (× 40) of anterior horn of L.3 in transverse section, showing concentration of argyrophile bodies in antero-medial region.

FIG. 2.—Low-power view (× 40) of sagittal section of L.3 showing distribution of argyrophile bodies between white matter and longitudinal column of motor neurons.

FIG. 3.—Argyrophile bodies in transverse section of S.1 (× 110).

FIG. 4.—Higher power view of Fig. 2 (× 110).

FIG. 5.—Argyrophile bodies in transverse section of L.3 lying among axons (× 325). In some a " stalk " appears to be present.

All photographs are from Gros-Bielschowsky preparations. Figs. 1, 2, *and* 4 *are counterstained with thionin.*

to a fair degree of inevitable tension at necropsy.

Further evidence regarding the absence of trauma to the lumbosacral nerve roots comes from the Marchi preparations from the same region of the cord. In nerve fibres subjected to post-mortem trauma a pseudo-Marchi reaction is constantly found. No such staining was ever observed in the area occupied by the argyrophile bodies, although there might be a marked degree of it in other parts of the central nervous system in the same case. If the myelin sheaths should show a reaction to pulling and other trauma it would seem probable that if any axons were damaged it would be those associated with the damaged myelin.

It would then appear to be unlikely that the bodies resulted from any post-mortem trauma of an avoidable nature.

FIG. 4

Silver Impregnation Artefacts.—Artefacts may occur in sections prepared by silver impregnation methods, but not in all cases in a constant distribution, nor do they have the same appearance as the argyrophile bodies.

Silver impregnation artefacts occur in the form of a scattered dust of small angulated particles throughout the section, giving a dirty appearance to the whole preparation, and obscuring the picture of the axons ; or they may be larger and concentrated intensely in one area, forming a dense black spot. Both forms are completely unlike the bodies described here.

Corpora Amylacea.—Corpora amylacea, in silver preparations, might be confused with the bodies, but their concentration in the white matter, their constant spherical appearance and free state, and their affinity for other stains render them clearly distinct.

FIG. 3

FIG. 5

Peculiarity in Impregnation Technique.—The possibility that the bodies represent a peculiarity of the impregnation technique is unlikely in view of the similar appearance they have in Gros-Bielschowsky and Holmes preparations. It may be noted also in this context that the appearance of these bodies was identical in sections prepared by different technicians.

No evidence in favour of regarding the argyrophile bodies as being artefacts has been obtained. Nevertheless, their affinity for the same stains as axons does suggest a relationship between them, and it is still considered possible that the bodies do represent some post-mortem alteration in certain axons, the cause of which has not been found.

Are these Bodies Pathological ?—The cause of death in the cases examined was varied. In about three-quarters of the cases cancer was a contributory final factor, but in the remaining cases death was due to other causes. The length of the final illness varied from no time at all (accident) to many months ; the general health of the patient at the time of death, and the degree of cachexia, if any, were also widely varied.

In the light of these facts it is difficult to see how structures of such a constant appearance and distribution could be caused by widely varied pathological conditions, in particular as they were found in every single case of a series, of which half were collected at random from the necropsy material in a general hospital.

When a nerve fibre is cut, or its continuity is otherwise interrupted, the central end of the axis cylinder forms a retraction ball. The argyrophile bodies described here undoubtedly resemble to some extent these retraction balls. But the absence of any other appearance suggesting a degeneration of axons, of myelin sheaths, or of neurons, at this site, would make it very unlikely that these argyrophile bodies do in fact indicate a lesion of axons.

It would appear then that the bodies are not pathological in nature, or, at least, are not consequent on a specific pathological condition.

Are they Anatomical ?—The argyrophile bodies have been found in every single cord of the large series examined ; they have also been seen in sections picked out at random from the silver preparations in three other laboratories. In all the cases they are localized to a limited region of grey matter of certain lumbosacral segments. This constant occurrence and restricted localization appear to support the view that the bodies are anatomical structures. The possibility that they are associated with the processes of ageing in the cord has been considered, but as they have been found in the cord of a healthy young man of 20 years this seems unlikely.

Conclusions

A discrete column of argyrophile bodies is present in the lumbosacral region in every cord examined from a series of 80 patients dying from a variety of pathological conditions.

These argyrophile bodies do not appear to be associated with any pathological process. The bodies stain in the same way as axons and lie among axons, and are therefore thought to be in some way related to them. Their constant occurrence may indicate that they are anatomical structures. There is no evidence that they are artefacts, nevertheless the possibility that they represent some post-mortem alteration in axons, probably of an unavoidable nature, has not been wholly excluded.

Unless it is recognized that these argyrophile bodies are a constant feature of adult human cords, their resemblance to the retraction balls seen after section of axons might lead to the misinterpretation that they indicate a lesion of axons.

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MORPHOLOGICAL NERVOUS CHANGES IN SURVIVORS OF SEVERE JAUNDICE OF THE NEWBORN

BY

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The clinical sequelae of Rh sensitization have been fully described by Pentschew (1948), Pickles (1949), and Evans and Polani (1950). The clinical variability of the condition is well known, but it tends to follow, nevertheless, a certain pattern. A stormy neonatal period with jaundice, drowsiness, feeding difficulties, opisthotonos, and respiratory disturbances is usually followed between the ages of 1 and 2 years by a "silent" period. After that, rigidity, intermittent opisthotonos, and involuntary movements make their appearance. Hypertonia may be present and this may be replaced by the intermittent spasms of athetosis. Involuntary choreiform movements may set in later, and deafness is also common. Mental defect is gross in some cases. In others a good level of intelligence is preserved though often masked by motor and sensory disabilities. The manifestations of Rh sensitization in mental defectives have been studied by Crome, Kirman, and Marrs (in preparation). Their findings correspond, on the whole, with those of other workers, a number of cases presenting a similar picture with athetosis, deafness, and a relatively well preserved mental capacity, though in other cases damage appears to be more extensive, even to the extent of complete idiocy.

These clinical manifestations are commonly regarded as being mainly "extrapyramidal", produced by lesions in the basal ganglia, viz., the globus pallidus and corpus Luysii. Such lesions have, in fact, been found in most of the recorded cases and given special prominence. Many of the authors have mentioned, however, the occurrence of other widely scattered abnormalities in the central nervous system. It is, indeed, possible that preoccupation with the readily detectable abnormalities in the basal ganglia has tended to obscure the more elusive widespread lesions in other areas, particularly in the cerebral cortex.

Knowledge of the structural changes caused by Rh sensitization rests, on the one hand, upon a large number of observations in patients dying in the neonatal period with hydrops foetalis or, more commonly, icterus gravis, and, on the other hand, on a small total of 17 morphological descriptions of cases of established residual kernicterus, some of which were of doubtful aetiology.

The structural changes found in the early fatal cases of Rh sensitization are characterized by generalized jaundice with staining by bilirubin of certain focal areas of the grey matter of the central nervous system, a blood picture marked by erythroblastosis and haemolysis, and some less constant findings in other organs such as persistence of haemopoietic foci in the liver and spleen, increase in size and weight of the liver and spleen, and the presence of iron-containing pigment and bilirubin in these organs (Bessis, 1946). The distribution of the stained foci in the central nervous system is very variable. Becker and Vogel (1948) have reviewed this problem well and supplied the following table of incidence in their own series : basal ganglia, 32 ; cerebellum, 25 ; medulla, 24 ; pallium, including hippocampus, 24 ; thalamus, 19 ; substantia nigra, 18 ; fourth ventricle, 18 ; meninges, 16 ; midbrain, 11 ; spinal cord, 10 ; ependyma, 9 ; hypothalamus, 8 ; choroid plexus, 7 ; epithalamus, 3 ; tela choroidea, 3 ; pons, 1. The histological changes in these cases of acute kernicterus have been inconstant. The wide gradation of degenerative processes in the nerve cells throughout the nervous system has been stressed by Bertrand (1946), who referred also to the considerable loss of nerve cells in the cerebral cortex.

It is probable that those infants who survive to develop neurological sequelae of residual kernicterus have similar, even if less marked, structural changes in the acute stages, because of the similarity of the clinical and laboratory features in the two groups of cases. The nuclear staining fades fairly rapidly and is usually absent after the first few weeks, but longer duration permits the appearance of later stages of other possible lesions. The recorded structural nervous changes in such cases are given in Table I.

TABLE I

CASES OF Rh FACTOR SENSITIZATION RECORDED IN THE LITERATURE

Case	Author	Age	Chief Clinical Features	Structural Changes
1	Hoffmann and Hausmann (1926)	3½ months	Icterus at 4 days, twitching, rotation of eyes, spasm of limbs, hypertonia, opisthotonos	Persistence of yellowish tinge in basal ganglia; other changes only microscopical: perivascular round-cell infiltration in basal ganglia and hippocampus; no definite nerve-cell changes; haemosiderosis of the liver
2	Burghard and Schleussing (1933)	5 months	Neonatal jaundice, yellow C.S.F., convulsions, opisthotonos at 5 days, hypertonia, early optic atrophy, development of generalized oedema, grimacing, squint, profuse sweating	Yellowish-grey staining of grey matter in pallidum, corpus Luysii, and Ammon's horn, lesser staining in other parts; some focal softening of white matter in both hemispheres; destruction of nerve cells with proliferation of glial cells, especially in hippocampus
3	de Lange (1934)	6 months	Neonatal jaundice, petit mal, hypertonia, opisthotonos, failure of development	Only basal ganglia examined. Lack of vertical striation in globus pallidus; loss of nerve cells in caudate nucleus, globus pallidus, and putamen; poor staining of myelin in globus pallidus and corpus Luysii
4	Zimmerman and Yannet (1935)	3 years	5 weeks premature, icterus gravis, rigidity, opisthotonos, optic atrophy after 5 months, athetosis, mental retardation	Demyelination of optic nerves, white matter around posterior horns of lateral ventricles, peripheral part of spinal cord; fascia dentata and endplate of lamina parietalis of hippocampus destroyed; loss of large nerve cells in corpus striatum and globus pallidus; absence of myelinated fibres in globus pallidus; corpus Luysii almost completely disappeared; paucity of nerve cells in red nuclei
5	de Lange (1935)	7½ months	One of twins both of whom had neonatal jaundice without erythroblastosis; hypertonia, rickets, retarded development	Yellow staining of flocculus, inferior olives, floor of fourth ventricle, Ammon's horn, thalamus, putamen, globus pallidus, and habenular nucleus; degeneration of nerve cells in inferior olives, globus pallidus, and putamen; iron and bile pigment in liver; cellular proliferation in portal tracts
6	de Lange (1936)	6 months	Neonatal jaundice, slight enlargement of liver and spleen, hypertonia, head retraction, rigidity	Absent striation of globus pallidus with loss of nerve cells; poor staining of myelin in globus pallidus and corpus Luysii; slight loss of cells in dentate nucleus; some deficiency of myelin in frontal and temporal lobes; corpus callosum and anterior commissure small; certain cytoarchitectonic abnormalities of cerebral cortex
7	Biemond and van Creveld (1937)	3 months	Neonatal jaundice and umbilical sepsis, rigidity, opisthotonos	Absent striation of globus pallidus; demyelination of globus pallidus and corpus Luysii; loss of nerve cells and gliosis in demyelinated areas; corpus callosum and fornices small
8		4 months	Neonatal jaundice and umbilical sepsis, slight anaemia, extrapyramidal signs with rigidity and opisthotonos	Slight yellow staining of globus pallidus and corpus Luysii; absent striation of globus pallidus; marked demyelination of globus pallidus and corpus Luysii with loss of nerve cells; corpus callosum and fornices small
9	Westrienen and de Lange (1937–38)	About 1 year	Icterus gravis, convulsions, opisthotonos, profuse sweating, clasp-knife rigidity	Blurred striation of globus pallidus with some shrinking of nerve cells and proliferation of glial cells; greater proliferation of glia in striatum; subthalamic nucleus small; poor staining of myelin in globus pallidus
10	Zimmerman (1938)	11 months	Neonatal jaundice, spasticity, head retraction, convulsions	Focal loss of nerve cells in caudate nucleus, putamen, dentate nucleus, inferior olives, and cerebral cortex
11	FitzGerald, Greenfield, and Kounine (1939)	4½ months	Neonatal jaundice	Bilateral sclerosis of globus pallidus with an almost total disappearance of nerve cells; considerable loss of nerve cells in corpus Luysii with dense fibrous gliosis; Ammon's horn and fascia dentata sclerosed
12		1 year	Neonatal jaundice	Basal ganglia, particularly the globus pallidus, shrunken and white; moderate cell loss in globus pallidus with poor staining of myelin; corpus Luysii sclerosed; appearance of cortical nerve cells suggestive of lack of differentiation
13	Sobel and Zucker (1940)	4½ years	Neonatal jaundice, erythroblastosis and anaemia, opisthotonos, spasticity, and choreo-athetosis	Moderate dilatation of ventricles; poor staining of myelin in globus pallidus and corpus Luysii; loss of myelin in pyramids; decrease in number of nerve cells in layers III and IV of cerebral cortex with proliferation of glia in cerebrum and diencephalon
14	van Bogaert (1947)	2½ years	Neonatal jaundice, opisthotonos, "decerebrate" position of upper limbs, development of choreo-athetosis	Atrophy of corpus Luysii and, to a lesser degree, of globus pallidus; slight degenerative changes in cerebral cortex
15	McLardy (1948)	2 years	Mother rhesus-negative; severe neonatal jaundice, very retarded development	Bilateral shrinking of globus pallidus with almost total demyelination and fibrous gliosis; conspicuous demyelination of large radial bundles of putamen and caudate nucleus; complete degeneration of corpus Luysii and degeneration of nerve cells in pyramidal layer and fascia dentata of hippocampus
16	Mann and Courville (1948)	7 months	Neonatal jaundice	Paucity of nerve cells in dentate nucleus, putamen, and globus pallidus; occasional perivascular sclerosis with increase of glia; many cells in substantia nigra vacuolated with indistinct outlines
17	Christensen and Vestergaard (1949)	22 years	Mental defective	Internal hydrocephalus; moderate atrophy of basal ganglia; peculiar microscopical yellowish pigment; some degeneration of nerve cells in cerebral cortex and Ammon's horn; softening in white matter

Most of the cases listed in Table I were examined before modern serological methods made diagnosis of rhesus factor sensitization possible. It is worth while therefore to record the following two further cases in which serological and clinical studies left little doubt as to rhesus factor incompatibility, icterus gravis neonatorum, and, presumably, kernicterus. Both occurred in a series of 140 consecutive necropsies of low-grade mental defectives at the Fountain Hospital.

In a third case, the issue of an incestuous union of brother and sister with rhesus factor incompatibility, neonatal jaundice and erythroblastosis foetalis were followed by complete idiocy, the pathological findings at necropsy being generalized lipoidosis occupying an intermediate position between Tay-Sachs and Niemann-Pick disease. This case presents a special problem and will be reported separately.

Case Reports

Case 1.—The patient was the second son of a rhesus-negative mother and a rhesus-positive father. There is no history of mental defect in the family. The mother was found to have Rh antibodies at about the thirty-seventh week of her first pregnancy, which preceded the second by two years, but the elder child's neonatal jaundice was mild, calling for no treatment, and his further development uneventful.

The mother's antibody titre rose to 1 in 1,000 some two months before the patient's birth and labour was induced at 36 weeks. The infant weighed 6 lb., his cord haemoglobin being 64% with a positive Coombs test. He was given an exchange transfusion by the umbilical vein, after which blood bilirubin was estimated at 9 mg. per 100 ml. The jaundice deepened the following day and another blood transfusion was given. After that it remained unchanged for some days, and gradually faded by the end of the first month. Fluctuating spasticity of the limbs appeared at the age of 2 months. At 5 months it was thought that he could hear and see, his head control was fairly good, and at 7 months he could grip things feebly and had his first tooth. A month later he was able to raise his hand to the mouth. His general health was reasonably good and weight gain satisfactory. At 10 months the mother sought further advice for the child's frequent prolonged crying fits.

At 15 months he was admitted to the Fountain Hospital as a temporary case. He was then accessible and cheerful, smiled when stroked, chuckled when tickled but made no sounds resembling speech. He smiled responsively to the ringing of a bell and so was not deaf. He followed objects with his eyes but made no attempt to reach for them ; he had a good grasp in either hand. He was intermittently rigid with occasional tremor in both arms and could not sit unsupported. His teeth were poor and yellowish and he had a double internal squint. The right side of the chest was flattened and he had an umbilical hernia. His developmental level was assessed at 3 months on the Vineland maturity scale, but this result was thought to be due in part to a specific motor handicap rather than to general retardation. A few weeks after admission he developed hyperpyrexia, 105° F., had generalized twitching and cyanosis, and died some hours later.

Pathological Findings.—Kyphoscoliosis and marked pigeon chest were the only visible deformities at necropsy. The subject weighed 9 kg., with height 90 cm. and head circumference 46·4 cm. The testes were in the inguinal canals, and the lungs showed a varied pattern of congestion, early consolidation, and lobular collapse, these changes being confirmed microscopically. The portal tracts of the liver contained a moderate amount of cellular exudate consisting chiefly of lymphocytes with a few polymorphs and plasma cells.

The only surface abnormality of the brain (1,050 g.) was congestion of the superficial veins. Coronal sections of the formalinized material showed reduction in size with absence of medullary pallidal lamination and slight discoloration of the globus pallidus anteriorly.

Coronal blocks of the frontal, parietal, temporal, and occipital lobes, the cerebellum, midbrain, pons, and medulla, together with representative levels of the spinal cord, were embedded in celloidin. Serial sections were cut of the basal ganglia on the left side. The usual neurological and general stains were employed, frozen sections being also used for scarlet R and Kulschitsky-Pal staining as well as for silver impregnation methods.

The two conspicuous structural changes were sparseness of cells in the superficial layers of the cerebral cortex and abnormality of the globus pallidus.

Cells were sparse in all areas of the cortex, being, possibly, more marked in the frontal and occipital lobes (Fig. 1). This sparseness was easily detectable in layers

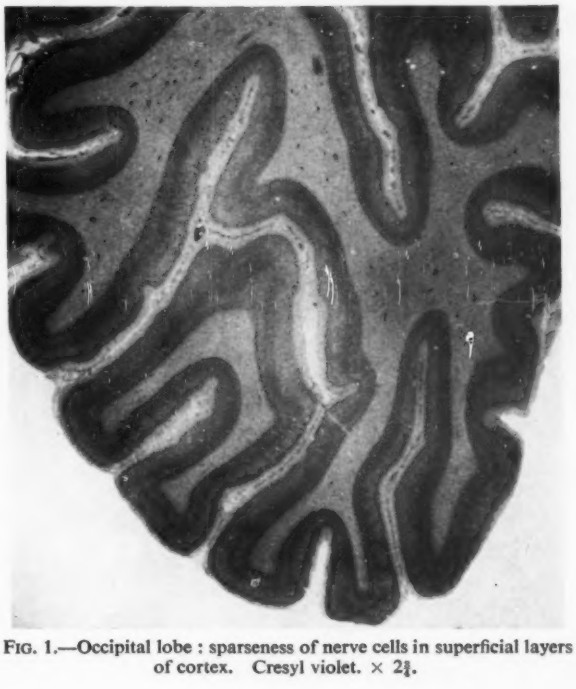

FIG. 1.—Occipital lobe : sparseness of nerve cells in superficial layers of cortex. Cresyl violet. × 2½.

FIG. 2.—Area 8 : loss of cells in layers II and III. Cresyl violet. × 27.

FIG. 3.—Basal ganglia : pallor of myelin in globus pallidus. Heidenhain. × 2½.

FIG. 4.—Globus pallidus : degeneration of myelin sheaths. Kulschitsky-Pal. × 550.

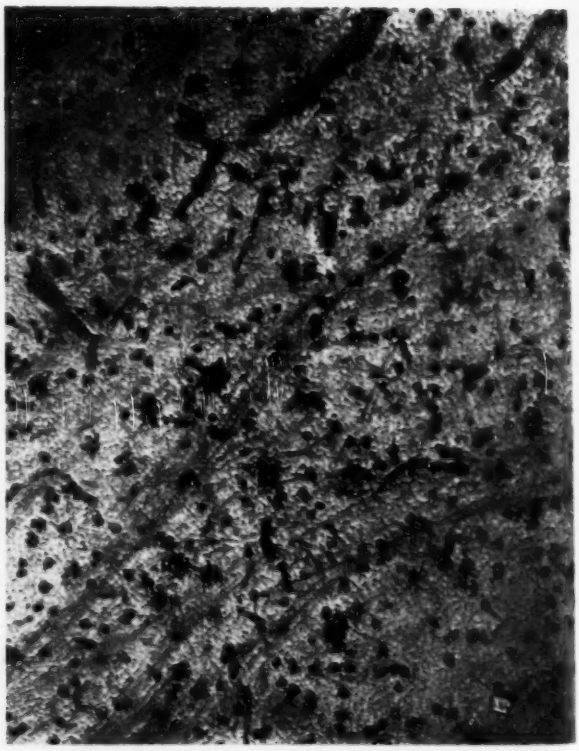

FIG. 5.—Globus pallidus : numerous particles of neutral fat. Herxheimer. × 160.

II and III (Fig. 2) but was probably also present in the deeper ones. The loss of cortical nerve cells was associated with degenerative changes in the remaining ones. These changes were not confined, however, to the cortex and will therefore be treated separately below.

The myelin in the anterior part of the globus pallidus was abnormally pale in sections stained by the Heidenhain and Kulschitsky-Pal methods (Fig. 3). There was also a conspicuous deficiency in the myelination of the large radial bundles in the putamen. Higher magnifications of the globus pallidus sections showed myelin sheaths in various stages of degeneration and breakdown (Fig. 4), consisting of tortuosity, focal ballooning, varicosity, uneven staining, and beading. Similar appearances were present in other parts of the nervous system, those in the globus pallidus being, however, more pronounced. Sections of this area stained by the Herxheimer method showed a much larger amount of neutral fat than in other places (Fig. 5). It was partly contained in compound granular corpuscles and endothelial capillary cells, and partly lay free in the tissue and in perivascular spaces. Some fibrous gliosis could also be demonstrated in the globus pallidus by the Holzer and the silver impregnation methods. The number of nerve cells was, however, only slightly reduced.

A small amount of cellular exudate was present in the meninges, consisting chiefly of lymphocytes and some macrophages containing yellow granular pigment.

Some foci of dense fibrous gliosis spreading from the surface to laminae I and II were found in the cerebral cortex; this was generalized in the hippocampus. Glial cells, consisting of microglia and fibrillary astrocytes, were slightly increased in number throughout the grey matter of the nervous system.

Nerve cells in the cerebral cortex and elsewhere stained very unevenly, some being hyper- and others hypo-chromatic. Their outlines were often irregular and indistinct with the cytoplasm vacuolated. Nissl substance was absent from all but the largest of them, and in those it tended to be broken into small particles and displaced peripherally. Many " ghost " forms could be seen.

A small amount of neutral fat was visible in all parts of the central nervous system, chiefly around capillaries, either free or in compound granular corpuscles and endothelial cells.

No other abnormality was found in the basal ganglia. The thalamic and subthalamic nuclei were, in particular, free from demonstrable change.

The only other noteworthy features were dense mural fibrous gliosis affecting the entire ventricular system and a semicircular layer of spongy degeneration situated midway between the outer pyramidal cells and the fascia dentata of the hippocampus.

Case 2.—The patient was the fourth child of a rhesus-negative mother and a rhesus-positive father. Two of the siblings, seven and five years older, were normal, the third died with neonatal jaundice three days after delivery, while the fifth and last pregnancy was terminated artificially. The mother had had a kidney removed before marriage and suffered from whooping cough during the patient's gestation. She and her husband were otherwise in good health. There is no history of mental defect in the family.

The pregnancy ended with a breech delivery about three weeks before term. The baby, weighing 1·6 kg., was limp and cried feebly. She was not immediately jaundiced, but Coombs's test was positive with haemoglobin 88% and nucleated red cells 29 per 100 W.B.C. A replacement transfusion was given the same day.

Jaundice appeared on the third day, when haemoglobin was 94%. On the sixth day twitching of limbs was observed, the head was retracted, the limbs spastic, and the body rigid. A lumbar puncture performed the following day yielded bile-stained fluid but no other abnormality. At 20 days, she had an attack of cyanosis with apnoea during a feed and was resuscitated with oxygen and coramine. She remained in poor general condition for a few days, having irregular respiration and feeding difficulty calling for tube feeding. After that she became anaemic with haemoglobin 68% on the twenty-second day and 48% on the thirty-third day. Examination of the bone marrow showed cellular active degeneration of normoblastic type with large numbers of primitive R.B.C.s, including pro-erythroblasts. A transfusion with 30 ml. of packed red cells was given at this stage, and two further transfusions with 38 ml. and 65 ml. of packed cells repeated at weekly intervals. The patient's general condition remained satisfactory, the haemoglobin rose to 80%, she gained weight, and was discharged at 2 months, taking the breast and supplementary feeds.

When seen six or seven months later she weighed 7 kg. and her mother complained that she was difficult to manage and cried frequently. She could not sit up. She was at that time spastic with choreo-athetotic movements. At 13 months she was seen again, and institutional treatment was recommended on account of her restlessness, poor sleep, and trouble at home.

On admission to the Fountain Hospital at 19 months she weighed 8 kg., with a head circumference of 41 cm. She could not talk, walk, sit, or do anything for herself. When an object was placed in her left hand she retained her grasp on it, but when anything was placed in her right hand she dropped it limply. She lay all the time in a position of marked opisthotonos and displayed very little spontaneous activity. She had generalized rigidity, athetoid movements, and a variable internal squint.

When a bell was rung, she stirred slightly and opened her eyes. She focused on brightly coloured objects and her eyes followed a pencil. She even made some effort to grasp objects with her right hand, but was handicapped in this by her incoordinated movements. She appeared to be of idiot level of intelligence.

Within three days of admission she developed bronchopneumonia, but recovered with penicillin and streptomycin treatment. The usual laboratory investigations, such as the Mantoux test, Wassermann reaction, blood and C.S.F. counts, were done, but added nothing significant. Her and her parents' blood groups are shown in Table II.

As both the father and patient were R_2r (positive) while the mother was Rh-negative and had anti-D in

TABLE II

BLOOD GROUPS OF CASE 2 AND HER PARENTS

	ABO	MNS	P	Rh	Lutheran	Kell	Lewis	Duffy	Kidd
Father	O	MNSs	P−	R_2r	Lu(a+)	K−	Le(a−b+)	Fy(a+)	J^k(a+)
Mother	O	MNSs	P+	rr	Lu(a−)	K−	Le(a−b+)	Fy(a−)	J^k(a−)
Patient	O	MNSs	P−	R_2r	Lu(a+)	K−	Le(a−b+)	Fy(a−)	J^k(a+)

her serum, the patient was probably a case of kernicterus due to rhesus incompatibility.

A month after admission to the Fountain Hospital, she went into status epilepticus, and died, in spite of all attempts to stop the convulsions, 30 hours later.

Pathological Findings.—Nothing noteworthy was found on naked-eye inspection in any organ other than the lungs, which showed some petechial pleural haemorrhages, pulmonary oedema, and congestion with small areas of lobular collapse in the lower lobes. Microscopical examination added nothing to the pulmonary findings.

FIG. 6.—Pallor of myelin in globus pallidus. Heidenhain. × 2¼.

The liver showed a slightly increased amount of fibrous tissue in the portal tracts.

The brain was small, 819 g. (normal, 1,050 g.), and the soft meninges were somewhat opaque, especially over the Sylvian fissure. The ventricular system was slightly dilated. The coronal blocks of the brain showed a barely perceptible bluish-brown discoloration of the globus pallidus and lack of definition in its outlines. The globus pallidus and the corpus Luysii were reduced in size and their outlines were somewhat indistinct.

Methods of histological examination of the central nervous system were as in Case 1 above.

The two main structural changes were closely similar to those of the first case: reduction in the number of cells in the superficial layers of the cerebral cortex and abnormality of the globus pallidus. The sparseness of cortical cells was, possibly, greater in the present case, while changes in the globus pallidus affected its components differently. The myelin was only slightly paler than normally (Fig. 6), although it presented many features of breakdown on higher magnification. The number of nerve cells in it was not appreciably reduced, while fibrous gliosis was more marked in the Holzer sections than in the first case. The corpus Luysii was, as mentioned above, somewhat reduced in size and the density of nerve cells in it slightly diminished.

Deficiency in the large radial bundles in the putamen was another mark of similarity with the first case.

The meninges showed a slight increase in collagenous connective tissue with a moderate cellular exudate of lymphocytes and fewer polymorphs. A uniform marginal fibrous gliosis extended over the whole of the cerebral cortex and brain-stem. The number of glial cells, astrocytes, and microglia was slightly increased throughout the grey matter. Some of the microglial cells were enlarged while others were phagocytic, containing, as in Case 1, a small quantity of neutral fat. The astrocytes were fibrillary in type.

Most of the nerve cells throughout the entire nervous system exhibited some degree of degenerative change. Those of the cerebral cortex presented mainly chromatolysis, shrinking, and transitional stages of homogenization with many "ghost" forms. Many of the cells in the subcortical centres showed similar changes, although these were less uniform. There was some focal loss in the Purkinje cerebellar cells, with feeble staining and swelling of the cytoplasm and nucleus in the remaining ones. Cells in the dentate and inferior olivary nuclei were also somewhat reduced in number, with many of the remaining ones showing degenerative change. Some of the large multipolar cells of the cranial nerve nuclei and anterior horns of the spinal cord showed chromatolysis and swelling of cytoplasm, while others were shrunken and their nuclei pyknotic.

Mural fibrous gliosis was present throughout the ventricular system. Scattered in the substance of the brain, spinal cord, and in the subarachnoid space were many small terminal haemorrhages with no fibrin or reactive changes around them.

Discussion

The two cases of the series correspond fairly closely with those recorded by earlier workers. The morphological changes in both of them were characterized by widespread loss of nerve cells in the cerebral cortex and by a more localized change in the globus pallidus. The significance of all the enumerated degenerative lesions in the nerve cells cannot be fully assessed; some of them may well have been caused by the terminal illness, especially in Case 2 marked by prolonged status epilepticus, others by post-mortem autolysis, and the remainder by the continuing effect of the basic pathogenetic factors responsible for the brunt of the damage.

The two main morphological changes are not specific for Rh sensitization. Loss of cortical nerve cells with ensuing laminar rarefaction is a common finding in the brain of low-grade mental defectives of many nosological groups. The globus pallidus is also a common seat of pathological processes, particularly those associated with anoxic states. It is true that cortical damage has not been mentioned in all of the previously recorded cases of residual kernicterus, but the reason for this may well have been the relative difficulty of its certain recognition, associated with the importance customarily attached to lesions in basal ganglia in extrapyramidal syndromes. It seems likely that it may be observed more frequently in similar cases if attention is paid to it in future studies.

Changes in the corpus Luysii were observed in Case 2 only. Deficiency in the large radial bundles of the putamen was present in Cases 1 and 2, but has been previously noted only by McLardy (1948).

It may be concluded, therefore, that the structural nervous changes in Rh sensitization are, like those of the acute kernicterus preceding it, widespread. They are characterized, in particular, by loss of nerve cells in the cerebral cortex and reduction in size, demyelination, and fibrous gliosis in the globus pallidus, and, more rarely, in the corpus Luysii.

Summary

The structural nervous changes in the recorded cases of neurological disease following severe jaundice of the newborn are reviewed and tabulated. A clinical and morbid-anatomical account is given of two further cases with serologically established rhesus factor incompatibility, neonatal jaundice, and erythroblastosis, both of which recovered from the initial acute condition to develop neurological disease. Changes in them were characterized by widespread cellular loss in the cerebral cortex with more focal lesions in the globus pallidus and, in one case, the corpus Luysii.

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UNUSUALLY SEVERE LESIONS IN THE BRAIN FOLLOWING STATUS EPILEPTICUS

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That severe convulsive seizures, especially if they occur in infancy and childhood, may lead to severe lesions in the brain has been known for some time and has been well demonstrated in Scholz's (1951) comprehensive monograph. The problem has acquired special importance through the recent hypothesis of Earle, Baldwin, and Penfield (1953), who maintain that atrophy of the anterior temporal lobe, particularly of the hippocampal gyrus and the first temporal convolution, may be caused in a large percentage of cases (63% of their total of 157) by a combination of herniation and anoxia at birth. This would imply that the Ammon's horn sclerosis would not be the sequel but the cause of at least temporal lobe seizures.

The present-day discussion on temporal lobe epilepsy has also demonstrated that despite a large number of publications on the histological findings in the brains of epileptics, it is not easy to learn precisely which regions are affected, apart from the Ammon's horn sclerosis, disseminated cerebellar sclerosis, and other regions on which special attention has been focused. Bateman (1936), mainly on macroscopic inspection, found atrophy or what he thought to be agenesis of the frontal lobe more marked than that of other lobes, and Scholz mentions that the lesions in the temporal regions, apart from Ammon's horn, were, perhaps, less severe. However, for the pathological investigation of temporal lobe epilepsy a more precise localization of lesions is necessary, and this will probably require either reinvestigation of old material or new post-mortem series including clinically and electrophysiologically well investigated cases which showed temporal lobe seizures during life. To our knowledge only two such investigations have been undertaken. Stauder (1935) found in material from 53 cases suitable for clinico-anatomical analysis a clear correlation between clinical signs of temporal lobe lesions and Ammon's horn sclerosis. Of 36 cases with positive Ammon's horn sclerosis, 29 exhibited definite temporal lobe symptomatology, whereas none of the 17 cases with normal Ammon's horn had shown such clinical features. Sano and Malamud (1953), in their clinico-anatomical analysis of 50 cases, arrived at similar conclusions. In neither investigation was any fuller pathological information provided.

The case which will be reported in this paper has already been briefly mentioned in a previous communication (Meyer, Falconer, and Beck, 1954). It seems to be of sufficient importance with regard to several problems concerning temporal lobe epilepsy to justify its publication as an individual case.

Clinical History

Gr. H. was born on November 1, 1939. He was admitted to hospital on October 1, 1948, being then aged 9 years.

The family history was of little significance. The mother, aged 40 at the date of his admission, was a war widow after three years of marriage. She had been over-solicitous of the child all his life and up to the time of his death refused to recognize the seriousness of his illness. The father had been killed in action as a pilot officer in 1941. He was described as healthy and good-natured. On the maternal side, the maternal grandmother was described as a normal personality; the maternal grandfather had been alcoholic and aggressive; there were five maternal collaterals in normal health. On the paternal side, the paternal grandmother was described as a difficult personality, and the paternal grandfather as a normal personality; there were no paternal collaterals.

Pregnancy and birth were normal, with a full-term delivery and a birth weight of 7½ lb. The baby was bottle fed. At 2 weeks of age he was circumcised and vaccinated. He was somewhat slow in walking and talking. At 4½ infected tonsils were removed. He had some nightmares thereafter. There had been no fits or convulsive phenomena in childhood. He was described by his mother as happy and healthy, but timid, dependent, and over-protected by her. He was enuretic till the age of 6, and subject to bronchitic colds. He went to a number of different schools and is said to have been slow to pick things up. He was right-handed. In his seventh year he had mild attacks of measles and mumps and was given injections against pertussis. He also suffered a mild attack of rubella when aged 8 years.

At the end of 1947, aged 8, he developed arthritis, swelling of the joints, wrists, and knees, transient rashes, and fever. On admission to The Hospital for Sick Children, Great Ormond Street, London, he had a leucocytosis of 21,000 (polymorphs 82%); the E.S.R. was 52 mm. in one hour. There were general glandular enlargement and splenomegaly. He gradually improved till April, 1948, when he relapsed with a sore throat and fever. There is a note that during treatment for the arthritis he had been receiving blood transfusions, the last of these on June 5, 1948. In July, 1948, splints were reapplied; his legs were put into plaster under rectal paraldehyde, a procedure which he underwent without any unusual reaction. Two days later generalized convulsions occurred lasting five hours, in spite of heavy sedation. His blood pressure was 210/120 mm. Hg, and albumin and casts were observed in the urine. He remained comatose for three days after the convulsions, during which time bilateral pneumonia developed: *Staph. aureus* and *B. influenzae* were grown from the sputum. He received sulphonamides, penicillin, and streptomycin, and was for four days in an oxygen tent. On recovery from the pneumonia he was found to be in a state of gross dementia. From that time onwards the mental state changed little until his death. In August, 1948, he developed jaundice, which was attributed to the earlier transfusions. Investigations at this time showed a normal cerebrospinal fluid; the Wassermann reaction was negative; no fracture was detected on radiographs of the lower extremities.

On transfer to the Maudsley Hospital on October 1, 1948, his general nutrition was poor. There was swelling of both elbows, knees, proximal interphalangeal and metatarsal joints. Movement was limited at the elbows, which appeared to be painful. The muscles were greatly wasted in the vicinity of the affected joints. The E.S.R. was 12 mm. in one minute and remained elevated during his stay in hospital. The pupils were dilated and reacted sluggishly to light, but there was no other abnormality on routine neurological examination. No abnormality was detected in the cardiovascular, respiratory, or alimentary systems. He was a bed patient, and was doubly incontinent. He appeared to recognize only his mother. He did not speak except on one unconfirmed occasion with a night nurse. From time to time he screamed without apparent purpose and when in pain or not. He fingered toys aimlessly and would hold a book upside down. He made ineffective efforts to feed himself and would put toys, sheets, and paper in his mouth and chew and dribble.

An E.E.G. taken on October 11, 1948, was abnormal, though the record was incomplete. Very little alpha rhythm was seen and the dominant rhythms were irregular, with fairly low voltage 2–7 c./sec. activity. In the frontal and central regions short bursts of 20 c./sec. were frequent and tended to become of fairly high voltage.

On October 26 convulsions began again and lasted for two and a half hours. They affected the right side more than the left, occasionally becoming generalized; the head and eyes turned rigidly to the right; the patient was cyanosed and his pupils were widely dilated.

On October 29 a note was made of periods characterized by sweating, dilated pupils, and tachycardia; screaming remained his most troublesome symptom. There was no significant change in the E.E.G. on November 5.

From November onwards the main therapeutic efforts were directed towards his physical rehabilitation. On February 16, 1949, he was able to walk the length of the ward and on March 8 to sit in the ward and show some interest in what was going on. On February 23 he suffered minor attacks, when he became flushed, halted in movement, and when eating dropped food from his mouth. Minor attacks of varied type continued to be noted up to five or six times daily. On May 12 fluttering of the eyelids, jerking of the limbs, and movement of the eyes to the right were observed. On May 19 there was noted spasm of the neck muscles, causing his head to drop on to his chest. There was a recurrence of status epilepticus on June 21, lasting several hours. On July 7 involuntary twitching and jerking of the shoulders, arms, and hands began; this continued during the night.

Pyrexia had recurred on May 2, marking the onset of the final phase of the illness. On May 14 there was evidence of consolidation at both lung bases. On June 7 a high remittent fever began. Bed sores became extensive, oedema of the ankles and ascites developed, and he died on August 2.

Post-mortem Investigation

The body was grossly wasted. There were severe decubital ulcers on the hips and sacrum. On opening the skull, the dura mater, blood sinuses, and cerebral blood vessels were found normal. The cerebrospinal fluid was increased. The meninges, particularly over the base, were slightly fibrosed. The brain and spinal cord were preserved uncut in 10% formalin.

Both pleurae showed old adhesions and there were also some old adhesions of the pericardium to the heart. No fluid was found. The lungs were collapsed and airless except for the bases, which were congested on both sides. The heart, aorta, and coronary arteries were normal. The abdomen contained no fluid or adhesions. The liver appeared to be slightly fatty. The spleen was enlarged, soft, and septic. The kidneys, which were of normal size, showed no definite macroscopic changes. Death was thought to be due to toxaemia from decubital ulcers.

Histological investigation of the organs showed cloudy swelling of the liver, heart muscle, and kidney. There were no Aschoff nodules in the heart. The spleen was congested; the pancreas and several mesenteric and cervical lymph glands were normal. The pituitary and adrenal glands showed no change save for terminal congestion and post-mortem change.

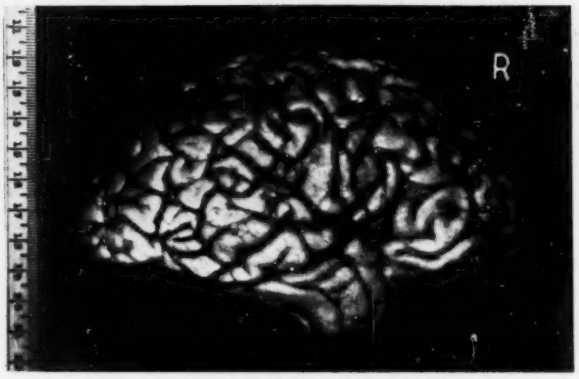

FIG. 1.—Lateral view of the right hemisphere.

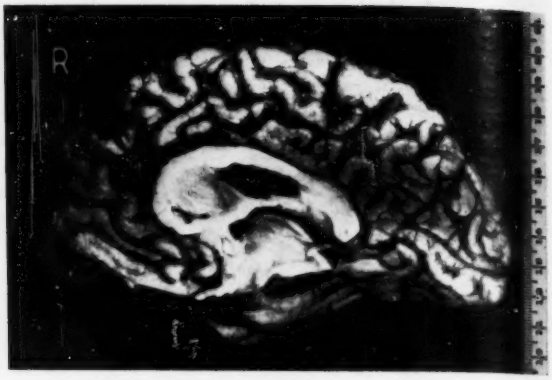

FIG. 2.—Medial view of the right hemisphere.

Macroscopic Description of the Brain

The brain weighed 1,160 g. No macroscopic abnormality was seen in the arteries at the base and convexity. The meninges generally were slightly thickened and opaque. There was definite symmetrical wasting of the convolutions (Figs. 1 and 2), most marked in the temporal lobes, which exhibited a peculiar shortened appearance, but almost equally marked in the frontal and particularly the medial orbital and anterior cingular regions. The parietal and occipital lobes and the posterior cingular region did not show any appreciable degree of atrophy.

Coronal dissection of the brain was still more informative. It showed, first, a considerable symmetrical enlargement of all ventricles including the inferior horn. Fig. 3 confirms the narrowness of the most medial orbital and the precallosal cingular convolutions; there was also varying atrophy of convolutions on the convexity. Fig. 4 brings out the narrowness of the cortex of the first temporal convolution as well as of the insula and the inferior frontal convolution. The amygdaloid nucleus is shown in Fig. 5 at its greatest extent and was found to be degenerated in its ventral parts. The corpus striatum was macroscopically intact, but the thalamus appeared abnormal and showed prominent blood vessels.

Fig. 6 presents a still more caudal coronal level of the temporal region. The superior temporal convolution is partially involved together with the insula and what is now supramarginal gyrus. Most of the remaining temporal convolutions are reduced in size, but the degeneration is most marked in the region around the collateral sulcus and in the hippocampal gyrus.

The localization of the lesions was almost identical in both hemispheres.

Coronal sections through more posterior levels of the parietal and occipital lobes did not reveal an appreciable degree of wasting.

The hypothalamus and the brain-stem were free from macroscopic lesions. The cerebellum showed atrophy of several lobules, particularly near the central white matter.

Histological Investigation

This confirms the macroscopic observations. The meninges were slightly fibrous; neither here nor elsewhere in the brain were there any perivascular inflammatory infiltrations. The adventitia of most arteries and veins of large or medium size was fibrosed, but despite careful search no abnormality was seen in the media or in the intima.

Within the temporal lobe the width of the cortex, as compared with normal temporal lobes, was generally reduced. In addition there were areas of focal lesions. In the Sylvian region the cortex of the inferior frontal convolution, the insula, and the superior temporal convolution was grossly disorganized. Most nerve cells had disappeared. There was an overgrowth of macroglial and microglial cells together with newly formed capillaries (Fig. 7). Only a few compound granular cells were seen. Mallory preparations showed a considerable proliferation of the fibrous glia extending from the marginal layer into the third layer. There was also heavy gliosis in the capsula extrema and the claustrum which showed partial loss of nerve cells and shrinkage of the remaining ones. There was, however, even in this area of greatest destruction of the cortex, a considerable amount of lipoids in microglial and adventitial histiocytes and probably also in proliferating astrocytes.

Leaving this area of almost complete destruction of the cortex, the middle and inferior temporal convolutions showed fairly well preserved cellular architecture, but with increased marginal and upper layer gliosis. In the cortex surrounding the collateral sulcus there was in the depth of the sulcus a laminary loss of nerve cells in the third layer, with

FIG. 3.—Coronal section through the anterior frontal region.

FIG. 4.—Coronal section at the level of the anterior commissure.

FIG. 5.—Coronal section through the greatest extent of the amygdaloid nucleus.

FIG. 6.—Coronal section at the level of Ammon's horn.

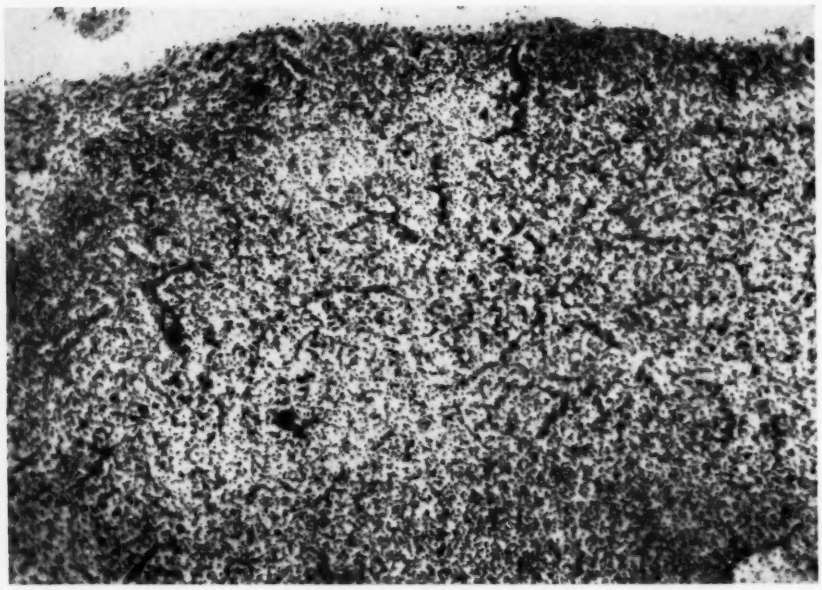

FIG. 7.—Insula cortex showing complete disorganization by loss of nerve cells and overgrowth of macro- and micro-glial cells and newly formed capillaries. Nissl stain. × 50.

FIG. 8.—Laminary loss of nerve cells in the third layer of the cortex surrounding the collateral sulcus. Nissl stain. × 15.

FIG. 9.—Ammon's horn sclerosis of Sommer sector and endplate. Nissl stain. × 10.

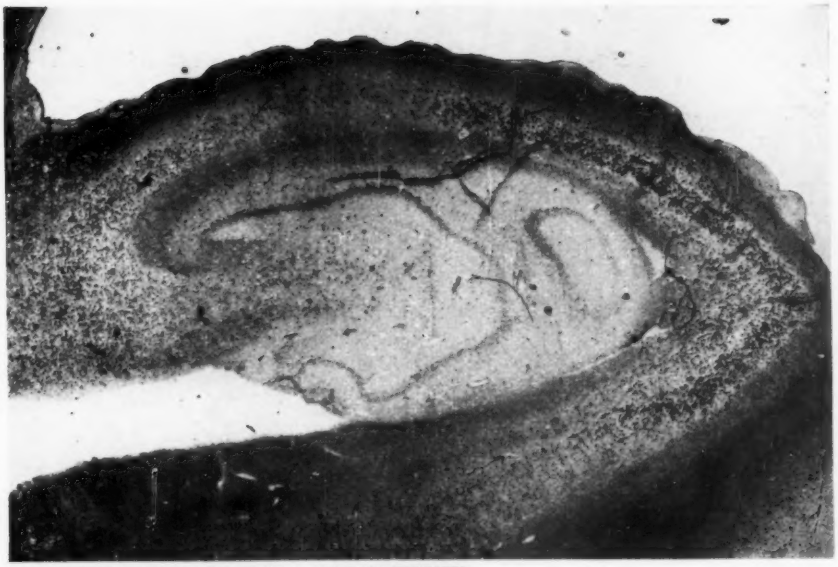

FIG. 10.—Ammon's horn ; considerable amount of lipoids in the Sommer sector mainly in microglial cells. Herxheimer's Scharlach R stain. × 10.

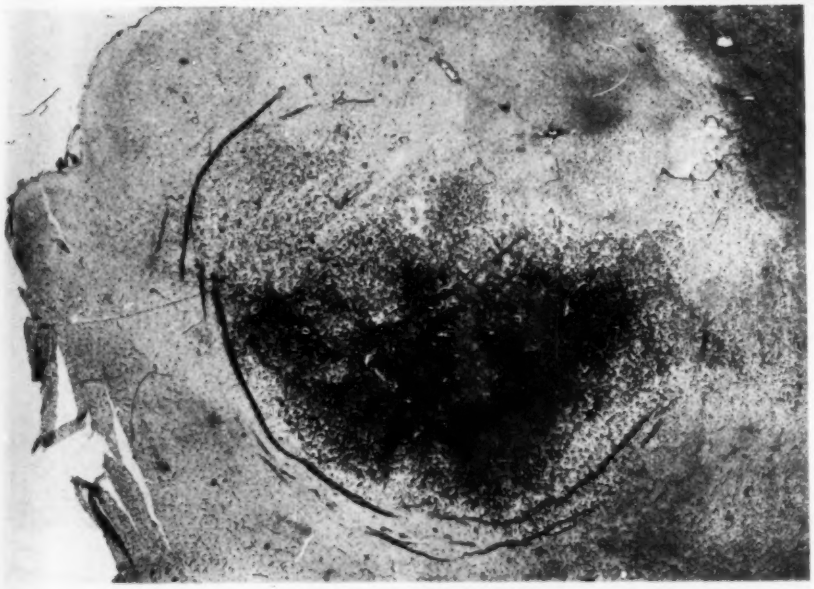

FIG. 11.—Amygdaloid nucleus ; considerable amount of lipoids in microglia and adventitial histiocytes and a few compound granular cells. The lesion is most marked in the ventral half of the nucleus. Herxheimer's Scharlach R stain. × 6·5.

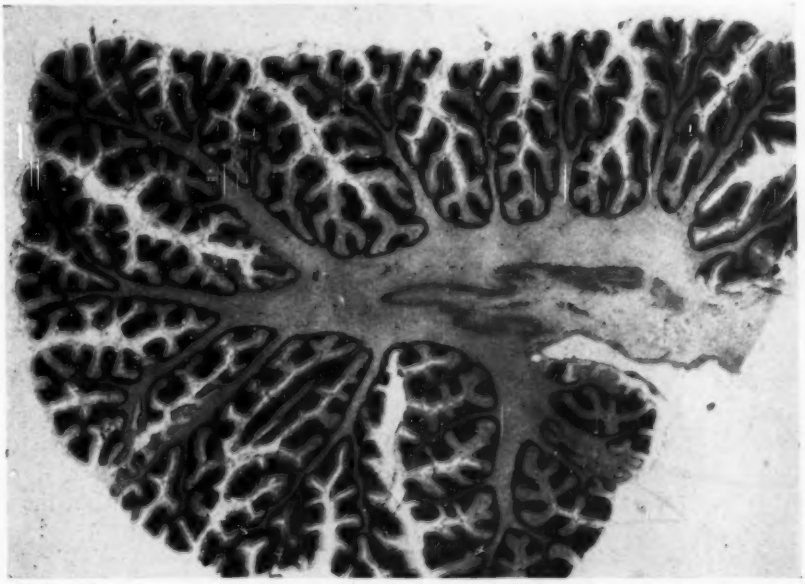

FIG. 12.—Disseminated lobular sclerosis of cerebellar cortex. Nissl stain. × 2·5.

corresponding microglial and macroglial overgrowth (Fig. 8) and intensive marginal gliosis and gliosis of the white matter. Still more medially a typical sclerosis of the Sommer sector and endplate of the cornu Ammonis was seen (Fig. 9). Fat staining revealed much lipoid in microglial histiocytes in the areas from which nerve cells had disappeared (Fig. 10). The lesion, which was identical on both sides, could be traced more anteriorly into the uncus. The amygdaloid nucleus in its ventral aspects showed extensive glio-mesodermal proliferation and lipoids in microglial cells, adventitial histiocytes, and in a few compound granular cells (Fig. 11).

Damage comparable to that in the Sylvian region was encountered in the mesial orbital and anterior cingular convolutions. There was extensive loss of neurons, particularly in the upper layers, with corresponding gliosis. The remaining frontal lobe showed similar changes, though of a lesser magnitude. Area 4 of Brodmann was narrower than normal, but the Betz cells were relatively spared.

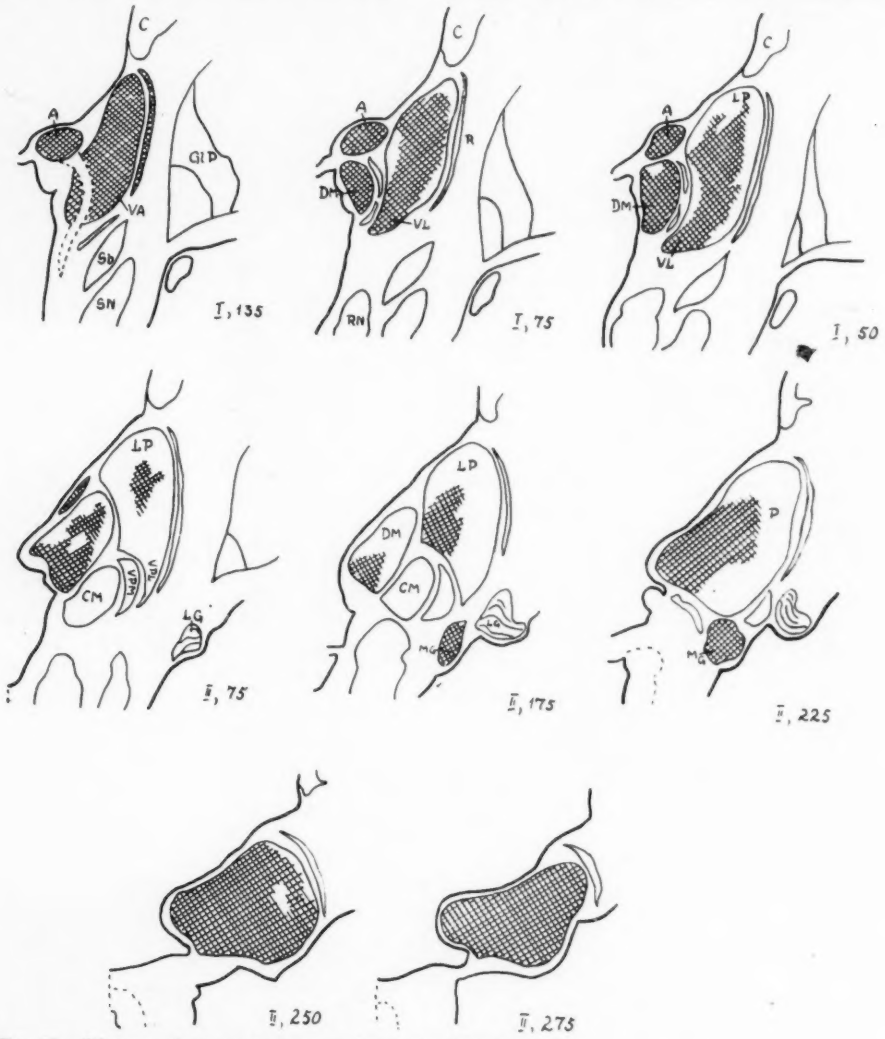

FIG. 13.—Diagram of retrograde degeneration in the right thalamus.

A :	nucleus anterior thalami.	R :	nucleus reticularis thalami.
C :	nucleus caudatus.	RN :	nucleus ruber.
CM :	nucleus centrum medianum.	Sb :	corpus subthalamicum.
DM :	nucleus medialis dorsalis thalami.	SN :	substantia nigra.
Gl P :	globus pallidus.	VA :	nucleus ventralis anterior thalami.
LG :	lateral geniculate.	VL :	nucleus ventralis lateralis thalami.
LP :	nucleus lateralis posterior thalami.	VPL :	nucleus ventralis postero-lateralis thalami.
MG :	medial geniculate.	VPM :	nucleus ventralis postero-medialis thalami.
P :	Pulvinar.		

The rest of the hemispheres showed only mild changes, exemplified by the occipital lobe, which demonstrated histologically slight diffuse neuronal loss and increased marginal gliosis without appreciable disturbance of the cytoarchitecture.

While the corpus striatum showed no histological changes the thalamus was grossly abnormal, as Fig. 13 indicates. From this diagram it is seen that the anterior nuclear group, including the rostral part of the reticular nucleus, nuclei ventralis anterior and ventralis lateralis, had degenerated almost completely. Of the dorso-medial nucleus only the dorsal portion of its posterior part had escaped. Only a relatively small antero-lateral part of the pulvinar was preserved. It should be noted, however, that even in the most afflicted nuclei some scattered shrunken nerve cells could, with higher magnification, be detected among the much proliferated macroglial and oligodendroglial nuclei.

The nucleus lateralis posterior was little affected. The posterior ventral nuclei were intact. The lateral geniculate body stood out in its normality against the completely degenerated medial geniculate body.

Against this background of widespread degeneration the intralaminary nuclei, including the centralis lateralis, paracentralis, and centro-median, were conspicuous by their normality save for the centralis medialis, the greater part of which had been destroyed in the heavily gliosed massa intermedia, possibly due to primary vascular or anoxic disturbance or to the direct pressure effect of the hydrocephalus of the third ventricle.

Most of the midline nuclei including the paraventricularis anterior, reuniens, and rhomboid could be identified. They were normal except for their most medial parts, which were involved in a particularly heavy subependymal gliosis.

The analysis of the retrograde degeneration was made in the thalamus of the right hemisphere. The left thalamus appeared to exhibit similar changes, but their analysis was confined to sample levels.

The subthalamus and the hypothalamus were intact.

The midbrain and the rest of the brain-stem were preserved. There was no demyelination of the pyramidal tracts, but in Nissl sections there was a definite gliosis. The inferior olives were intact. The cerebellar cortex, however, particularly in the area near the central white matter, showed disseminated lobular atrophy (Fig. 12).

Discussion

Clinically, this was the case of a child whose first serious illness was that of Still's disease at the age of 9. During the course of treatment in hospital he suddenly and for no obvious reason went into status epilepticus ; this was followed by a three-day period of unconsciousness and then by a pneumonia; on recovery from the infection he was found to be severely demented. His mental state failed to improve during his remaining year of life, in the course of which minor, temporal lobe, and major seizures were observed. He died of toxaemia associated with decubital ulcers.

The pathological investigation has not entirely clarified the immediate cause of the first serial epileptic attacks. Towards the end of 1947 the patient showed the first symptoms of Still's syndrome. Earlier in that year he had also had rubella. Measles, mumps, and injections against pertussis were recorded in 1946. Against the arthritis he had been receiving blood transfusions, the last on June 5, 1948, that is, more than a month before the onset of the convulsions. The jaundice which developed in August, 1948, was attributed at the time to these transfusions. The application of plaster to the legs under rectal paraldehyde preceded the onset of status epilepticus by two days and was unremarkable. There would therefore seem to be no obvious nexus between the convulsions and any single preceding event in the medical history.

Whatever may have been the cause of the epilepsy, no sign of inflammatory reaction was found in the central nervous system. The arteries and veins, including the dural sinuses, were macroscopically normal, and histologically, despite careful search, no allergic or other abnormality could be detected in the blood-vessel walls, not even those minor changes which Meyer (1953) described as the sequelae of previous thrombosis. Thus this case is probably one more example confirming the often stated fact that particularly severe epileptic convulsions may be precipitated by childhood fevers, acute gastric infections, and allergic conditions in infancy and early childhood (Scholz, 1953 ; Meyer, 1953), although the exact pathogenic mechanism is not yet known. It is possible that the severe pneumonia which followed the status epilepticus may have been an important auxiliary pathogenic factor in the production of the lesions.

The lesions in the brain were clearly the consequence of circulatory disturbance or anoxia. They consisted of selective parenchymal degeneration (Scholz, 1949) in most areas, frequently confined to the third layer and to the depth of the sulcus. Only in areas of most severe affection, as, for example, had occurred in the convolutions surrounding the Sylvian fissure, was the whole of the cortex involved : the lesions resembled incomplete softenings. The

Ammon's horn sclerosis and the disseminated cerebellar sclerosis were typical of lesions frequently found in brains of epileptics.

Particular attention has been paid to the age of the lesions. In all cortical necrotic areas there was still a considerable amount of lipoidal breakdown products within histiocytic elements which only rarely had progressed to the stage of granular compound cells. In our opinion none of the lesions could have been older than just over 12 months, i.e., than the first status epilepticus which had resulted in dementia. Some could have been of even more recent origin, probably caused by later recurrences of serial attacks.

The main interest of the case lies in the distribution of the lesions. In the first place, the emphasis is on the temporal lobe and the adjacent Sylvian region including the insula. This is of interest, since a proportion of the minor seizures which followed the generalized convulsions were of a type which would be described as temporal lobe seizures, particularly the screaming and flushing attacks. The electroencephalographic changes were, however, more severe and widespread than would be expected in temporal lobe epilepsy. This finding is in accordance with the wide distribution of pathological changes outside the temporal lobes. No special application of electrodes was practised at the time of the examination.

From Figs. 4 to 6 it is clear that the emphasis of the severity of lesions within the temporal lobe is on the first temporal convolution and the medial convolutions including the hippocampus, i.e., in the same areas which Earle, Baldwin, and Penfield (1953) regarded as particularly vulnerable during tentorial herniation and anoxia at birth. Their occurrence in our case demonstrates that this pathogenic mechanism is not exclusive for injury at birth but may occur in other conditions including status epilepticus itself. One of us (Meyer, 1939) has drawn attention to the importance of uncal pressure cone as an additional factor in the production of Ammon's horn sclerosis following epileptic seizures and has referred to a paper by Hasenjäger and Spatz (1937), who described the most characteristic uncal pressure cone of their series in a patient dying in status epilepticus.

Of the lesions in subcortical centres the one in the thalamus proved to be attributable mainly to retrograde degeneration. Its completeness, particularly in the anterior and anterior ventral nuclei, was surprising in view of the relatively well preserved posterior parts of the cingular gyrus and the widely expressed belief that the anterior ventral nucleus does not project on to the cortex. Perhaps this discrepancy may be resolved by the assumption that there may have been also some direct vascular damage to these nuclei in addition to the retrograde degeneration. Scholz (1951) has described vascular and anoxic lesions in the thalamus which occurred with particular frequency in the region of the anterior and lateral nuclei (*vide* his Fig. 26).

The fact that the system of intralaminary nuclei, including the centro-median nucleus, was almost entirely intact demonstrates that the greater part of the thalamic lesion must have been due to retrograde degeneration. Only the nucleus centralis medialis was found to be degenerated in the massa intermedia, which was probably directly damaged. It is idle to speculate in this case to what extent the thalamic reticular system was functionally involved in the mechanism of the minor and temporal lobe seizures, and, if so, which pathways would be available for impulses arising in this system. Impulses could hardly have been conveyed by the dorso-medial and anterior projection nuclei to the frontal region. The nucleus ventralis anterior and the rostral portion of the reticular nuclei which, according to Hanbery and Jasper (1953, 1954), collect and convey the impulses of the ascending reticular system, were also heavily damaged. Impulses could have been conveyed from the intact centro-median nucleus to the undamaged striate body (Droogleever-Fortuyn and Stefens, 1951), but their further passage to the frontal cortex through a largely degenerated thalamus would have been difficult. There would remain the possibility of circuitous pathways including an extra-thalamic pathway involving direct passage from the hypothalamic and subthalamic portion of the reticular system into the internal capsule (Starzl, Taylor, and Magoun, 1951). Although this discussion of the part played by the intralaminary system must remain inconclusive, it does demonstrate some of the unexpected difficulties of interpretation encountered in individual cases.

It was interesting to note that in the posterior plane of the dorso-medial nucleus the dorsal part was intact, thus confirming McLardy's (1950) finding that this part of the nucleus does not partake in the projection to the frontal lobe. The extensive retrograde degeneration of the pulvinar is explained by the considerable extent of the lesion in the temporal lobe, particularly in its caudal levels, as well as by that in the supramarginal gyrus. It is not possible to say whether the degeneration of the temporal pole had also contributed to the retrograde change in the pulvinar (Simpson, 1952). The fairly severe degeneration and gliosis of the claustrum which accompanied the softening of the insula had no retrograde effect upon the centro-median

nucleus ; this observation should finally remove any lingering doubts concerning a projection of this nucleus to the claustrum (McLardy, 1948).

The softening in the ventral parts of the amygdaloid nucleus, which was bilateral, is illustrated in Figs. 5 and 11, and is, so far as we can make out, the first observation of such a lesion in epileptic brains. Brockhaus (1939) described status marmoratus in the amygdaloid nucleus in two cases (Cases 4 and 5 of his series) of congenital and early infantile disease, but the relation to epilepsy was not clear. Since our attention has been drawn to the possibility of an amygdaloid lesion, we have been able to observe it as a post-epileptic phenomenon in several cases which include epilepsy from childhood and epilepsy caused by prefrontal leucotomy. In all but one the amygdaloid lesion was associated with severe sclerosis of Ammon's horn and the uncus.

A full account of these new findings will be given when the histological investigation in all cases is complete and the rate of incidence of amygdaloid lesions known. Until then there can be only reserved comment upon the possible repercussion of the observations in the amygdaloid nucleus upon the much-discussed and still intractable problem of the selective vulnerability and the functional significance of Ammon's horn.

Ammon's horn receives its vascular supply from the anterior choroidal artery, which also supplies the uncus, the amygdaloid nucleus, and the globus pallidus (Abbie, 1933 ; Alexander, 1942a and b). Interference with the blood supply confined to the more anterior branches which go to the hippocampus and amygdaloid nucleus would explain the necrosis of these centres, while the globus pallidus, which is supplied by posterior branches, remains unaffected. Uncal herniation as suggested by Penfield and his associates might commend itself as an event having such localized effect. It has been mentioned earlier in this discussion that uncal herniation, probably as a consequence of concomitant oedema, has been observed after death in status epilepticus.

Ammon's horn, the uncus, and the amygdaloid nucleus are also prominent members of the so-called visceral brain, which they form together with the anterior insula, posterior orbital and anterior cingular regions. Knowledge of the function of the visceral brain is still fragmentary and controversial, but if, as is now widely held, Ammon's horn and the amygdaloid nucleus play an active part in epileptic discharges in general, or at least in certain forms of epilepsy, then these centres would be, in a situation of general anoxia, more easily exhausted and succumb more readily to consumptive anoxia (Scholz, 1953). It is perhaps more than a coincidence that in our case all the regions of the visceral brain were severely damaged.

However, a full discussion of these intriguing aspects must wait until all the facts are marshalled.

Summary

The case has been described of a boy who at the age of 9 became ill with Still's syndrome. In the course of this illness he suddenly went into status epilepticus, which was followed by three days' coma and pneumonia. On recovery from the acute episode he was found to be demented. Subsequently he had grand mal, petit mal, and also what may be described as temporal lobe seizures. He died 12 months after the first epileptic seizure.

At necropsy he showed widespread damage in the brain due mainly to circulatory and anoxic disturbances associated with the first status epilepticus. The lesions were most severe in the first temporal convolution and adjacent Sylvian regions, Ammon's horn and the hippocampal gyrus, the medial orbital and the anterior cingular regions. The amygdaloid nucleus showed extensive incomplete softening.

The pathogenesis and functional significance of the lesions are discussed. Particular attention is drawn to the combination of lesions in the first temporal convolution and hippocampus, which Earle, Baldwin, and Penfield regarded as specific to herniation and anoxia at birth.

Special reference is made to the involvement of the amygdaloid nucleus.

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PREFRONTAL LEUCOTOMY AND THE ANTICIPATION OF PAIN

BY

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Preliminary observations (Elithorn, Piercy, and Crosskey, 1954 a and b) on patients undergoing prefrontal leucotomy revealed changes in autonomic function following the operation, and it was suggested that these were largely due to a reduction in the abnormal autonomic activity which accompanied the pre-operative mental disturbance. Similar views have been expressed by other workers (Carscallen, Buck, and Hobbs, 1951 ; Conklin, 1951). Solomon and Greenblatt (1953) also report that patients improved by leucotomy showed a physiological improvement in their blood-pressure responses to intravenous mecholyl. They appear, however, to regard the physiological changes as causative rather than as secondary to psychological improvement.

Since our own observations and those of others suggested that the frontal areas damaged by leucotomy contained no primary vegetative centres an attempt was made to devise a test which would measure autonomic changes which could be interpreted in terms of the psychological effects of leucotomy. A typical effect of a prefrontal destructive lesion, whether therapeutic or accidental, is an apparent reduction in the patient's feelings of anxiety. Further, an early paradoxical observation was that patients who suffered from severe pain, organic in origin, might be relieved of their suffering although their perception of pain remained unimpaired (Chapman, Rose, and Solomon, 1948). With a view therefore to analysing further the changed attitude to pain which follows prefrontal leucotomy the following test procedure was devised.

Methods

Autonomic reaction was measured in terms of the change in the electrical resistance of the palmar skin accompanying alteration in the rate of sweating (psychogalvanic reflex). Responses were measured to two stimuli : an electrical stimulus and a red light which was regularly exhibited for a short interval 7 seconds before the start of the electrical stimulus. Successive electrical stimuli were increased in intensity in steps of 2·5 volts from a subliminal value to the maximum intensity which the subject was prepared to tolerate. Measurements were also taken of the resting level of skin resistance, responses to maximal inspirations and to a sudden loud noise, the smallest perceptible electrical stimulus, and the maximum stimulus tolerated. At the end of the experiment responses to the red light were measured after the subject had been told that there would be no further electrical stimuli.

The size of the psychogalvanic reflex depends not only on the immediate stimulus but also on such factors as the time of day, the season, environmental temperature, mood, and the presence or absence of psychiatric disease (Richter, 1929 ; Conklin, 1951). Our observations were made at the temperature prevailing in the laboratory. Consequently, no emphasis is placed on the absolute values of the observed responses. However, overall changes in autonomic reactivity would not be expected to have much effect on the proportional relationship between the responses to two different stimuli unless the significance of one stimulus changed in relation to the other. Accordingly we studied the ratio of the response following the electrical stimulus to the response following the warning red light.

Procedure

The apparatus used for recording the psychogalvanic responses and for administering the electrical stimuli has been described elsewhere (Elithorn and others, 1954a). Fig. 1 shows sample records.

Each test session lasted about 50 minutes and was divided into three roughly equal parts. Before each part the procedure was explained to the patient who was comfortably seated throughout with the arms supported on rests.

During part one the subject rested quietly while the electrodes were applied and then measurements were made of the resting skin temperature and skin

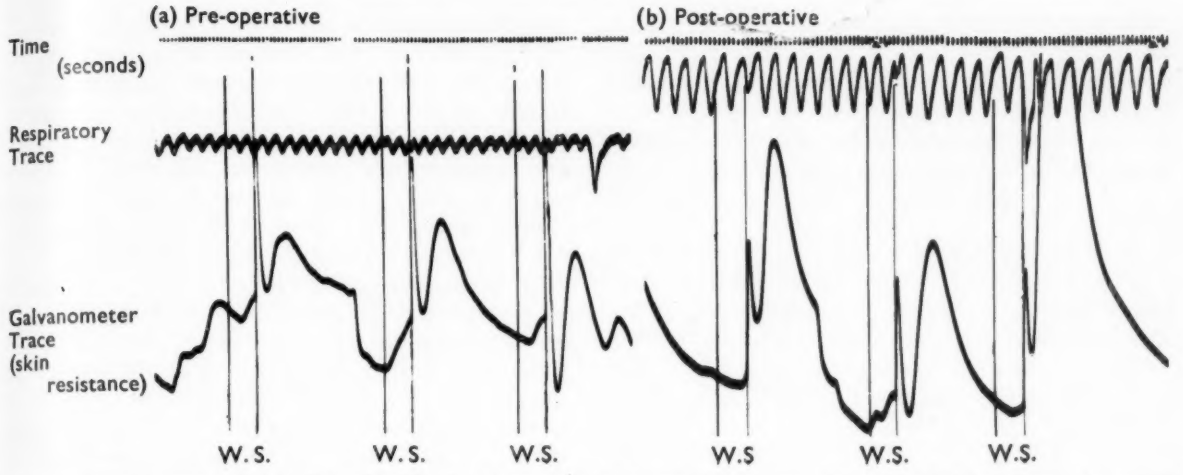

FIG. 1.—Sample records obtained with subject C. G. (a) six days before and (b) 236 days after a modified leucotomy. An upward deflection of the galvanometer trace corresponds to a fall in skin resistance. A rise of 1 cm. is equivalent in (a) to a fall of $2{\cdot}0 \times 10^3$ ohms and in (b) to a fall of $2{\cdot}3 \times 10^3$ ohms. The vertical lines mark the time of presentation of the warning light (W) and of the shocks (S). In both records the stimuli shown are the three occurring immediately before the subject said "Stop". The disturbance in the galvanic trace during the exhibition of the shock is due to stimuli escape.

resistance. A short recording was then made of the spontaneous changes in skin resistance which took place while the subject was resting and after this the responses to three maximal inspirations and a sudden noise were recorded. The resting skin resistance and skin temperature were then measured again. In part two the subject's sensations were tested: first, on each hand, the strength of shock which he could just detect was measured (the shocks lasted for 400 milliseconds and each consisted of a series of square pulses with a duration of 70 milliseconds and a frequency of 100 a second). He was then told that the shock on the right hand was going to be increased gradually until it became painful. The subject was instructed to say "Stop" when it became as painful as he could bear and he was assured that as soon as he said this the shock would be turned off. It was pointed out that the shock would cause no damage and that it would stop as soon as he said "Stop". Apprehensive patients were encouraged to do their best; stoics and others were instructed not to martyr themselves but to say "Stop" when the pain was more than they could reasonably bear. Following these instructions the shock was reapplied to the right hand and was increased in strength in units of 2·5 volts each second until the subject said "Stop". This was repeated twice with the interval between shocks increased to approximately five seconds and then once again with shocks every second (with both time intervals the shock duration as for the perception test was approximately 400 milliseconds).

The strength of shock which the subject was receiving when he said "Stop" was recorded as the refusal level and the ratio of this to the perceptual level was designated the "pain tolerance ratio". When the four estimates of the pain tolerance ratio had been obtained, the subject was told to rest and part three of the test was explained. In part three a final series of shocks was exhibited. Each shock was of the same character and duration as before and each was 2·5 v. stronger than its predecessor. The strength of the first shock was, however, so chosen that approximately the first three stimuli would be below the subject's observed threshold of perception. The shocks were separated by an interval which was never less than 15 seconds and rarely more than 40. Further, seven seconds before each shock a red warning light was exhibited, the significance of which was explained clearly to the subject, who was told to say "Red" whenever he saw the red light, "Right" whenever he felt the shock in his right hand, and "Stop" when the shocks became too strong. When the shock series had been brought to an end by the subject saying "Stop" he was told that there would be no more shocks, that we had nearly finished and that he would be shown a few more red lights, to which he must respond "Red" but that these would not be followed by a shock. Throughout the light shock series the psychogalvanic responses to each stimulus were recorded from the left hand (sample records are given in Fig. 1). At the end of the series resting-levels of skin resistance and skin temperature were again recorded. The effects of leucotomy on resting skin resistance and resting skin temperature have been reported elsewhere (Elithorn and others, 1954b) and call for no further

comment. Preliminary experiments had shown that many subjects, and in particular psychiatric patients, had difficulty in determining a point at which the shock stimulus became painful. The point at which the stimulus became "too painful" was much more consistently judged and some preliminary experiments reported elsewhere (Elithorn and others, 1950) gave a test-retest correlation coefficient of 0·89 ($p<0·001$) for the pain tolerance ratio. The results obtained also seemed to bear a reasonable relationship to the clinical evaluation of the patient's attitude to pain (Table I). The pain tolerance ratios reported here are derived from the mean perception threshold for the right hand and the mean of the two refusal levels for the right hand observed when the shock was repeated once a second. The expectancy situation—part three—was designed to test the hypothesis that after leucotomy there would be a disruption of the relationship between the autonomic disturbance caused by the anticipation of pain and that caused by the pain itself. The procedure was not designed to test the formation of a conditioned reflex, but since the test shows some similarities to conditioning procedures, it was decided to show the subjects a few identical lights at the end of the expectancy run to make sure that conditioning had not occurred.

Subjects

Brief clinical details of the patients investigated are given in Table I. Fuller clinical summaries

TABLE I

CLINICAL SUMMARIES OF PATIENTS INVESTIGATED

Subject	Hospital No.	Sex	Age	Diagnosis	Type of Operation	Effect of Operation on Psychiatric State	Pain Tolerance (threshold units)		Expectancy (Shock-light) Ratio			Time of Final Session in Months after Operation
							Mean Value Pre-op.	Mean Value Post-op.	Mean Value Pre-op.	Mean Value Post-op.	Value Observed at Final Session	
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)
A.K.	23166	M	48	Paranoid involutional depression	Standard leucotomy	Recovered	7·4	6·6	4·9	10·8	6·5	5
A.C.	19179	M	50	Cystic lung with hypochondriasis, thoracoplasty pain in the chest, and hysteria	Standard leucotomy	Improved	2·2	2·1	2·7	10·0	23·5	5
C.G.	25458	F	50	Paraphrenia	Standard leucotomy	Much improved	4·2	4·2	2·2	3·5	7·0	9
A.M.	14765	M	56	Cerebral arteriosclerosis, involutional depression	Standard leucotomy	Much improved	3·7	2·5	13·4	28·0	19·2	13
J.P.	8143	M	41	Post-encephalitic dystonia with pain, depression, and hysteria	Standard leucotomy	Much improved	1·7	1·5	—	—	—	—
E.S.	18957	F	53	Post-herpetic neuralgia, reactive depression	Unilateral leucotomy	Marked but transient improvement	4·7	4·5	1·7	5·2	4·3	18
L.B.	29566	F	44	Disseminated sclerosis with severe central pain	Unilateral leucotomy	Marked but transient improvement	2·1	3·5	3·4	4·2	4·9	3
H.W.	25598	M	56	Post-herpetic neuralgia, depression	Rostral leucotomy (with secondary thrombosis)	Very much improved	3·2	3·8	4·2	38·5	6·1	11
J.H.	28174	M	50	Tinnitus, endogenous depression	Rostral leucotomy	Much improved	2·5	2·9	2·9	7·5	2·7	20
W.H.	22074	F	37	Chronic anxiety state	Rostral leucotomy	Improved	7·3	7·1	4·7	11·5	11·7	13
A.S.	11773	M	46	Obsessional neurosis, chronic anxiety state	Rostral leucotomy	Much improved	—	—	2·3	4·9	3·3	7
G.P.	25908	M	65	Chronic anxiety state, involutional hypochondriasis	Lower segment leucotomy	Transient improvement	2·5	2·4	5·0	14·1	1·9	4
M.D.	16575	M	41	Hypochondriasis	Cingulectomy	Improved	4·1	5·1	4·9	4·2	4·4	18
J.G.	27508	M	43	Inadequate personality, chronic anxiety state, depression	Cingulectomy	Much improved	3·8	4·5	3·7	6·0	2·1	6

will be published elsewhere. The only criterion of selection used was the availability of the patient for pre-operative testing.

Results

Pain Tolerance.—The mean pre-operative and mean post-operative values for the pain tolerance ratios are given in Table I. The effect of the operation on the toleration of this particular painful stimulus is very small. Following leucotomy, tolerance is increased in six subjects and reduced in six subjects. For subject C. G. the post-operative value was the same as that found pre-operatively. Subject A. S., who was obsessional and had a high skin resistance, always tolerated as strong a shock as we were able to provide. Consequently we have no data as to the effect of leucotomy on his pain tolerance. Fig. 2, in which the pre-operative and post-operative pain tolerance ratios are plotted

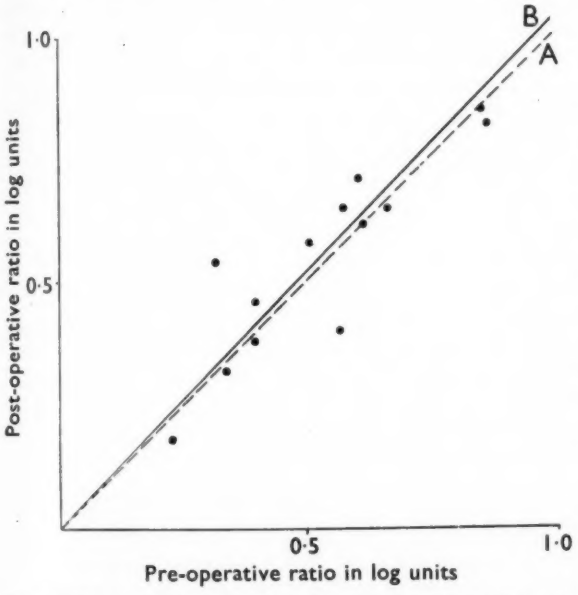

FIG. 2.—The observed relationships between the post-operative pain tolerance ratio and that found pre-operatively is represented by the line B which has the form $\log y = 1{\cdot}03 \log x$. This is not significantly different from line A which represents no change.

in logarithmic units, presents these findings graphically. In Fig. 2 the line A is that on which hypothetical observations would fall if the ratios found post-operatively were the same for each subject as those found pre-operatively. The observed values do, in fact, lie about this line, the mean observed relationship between the pre-operative and post-operative findings being represented by the line B. Student's "t" test (Fisher, 1942), using these logarithmic values, shows that the post-operative ratios are not significantly different from those found pre-operatively ($t = 0{\cdot}55$ $n = 12$, $p > 0{\cdot}5$). It is clear, therefore, that this ratio is a repeatable observation measuring a pain tolerance which is different in different subjects and which is not significantly changed when the test is repeated after a full or modified leucotomy.

Autonomic Responses.—Day-to-day variations in the psychogalvanic responses resulting from environmental conditions were large, relative to any overall effect due to the operation. Indeed, as previously reported (Elithorn and others, 1954b), the operation appeared to affect the overall responsiveness in opposite directions in different patients. For the group as a whole the post-operative responses to both the light and the shock tended to be lower than those found pre-operatively, but this change was not significant. However, as we have argued, much of this day-to-day variation is excluded if we consider the relationship between the responses to the shocks and the responses to the warning lights rather than their absolute values. This relationship can be conveniently expressed by the ratio of the mean shock response to the mean light response. We may call this the "expectancy ratio". This statistic has been calculated for each patient on each test session. In Table I the mean values pre-operatively and post-operatively are presented (columns 10 and 11) together with the value found on the last occasion on which each patient was tested (column 12). The time between operation and the final examination is also given (column 13). It will be seen that post-operatively the mean ratio was increased in 12 out of 13 subjects. Further, in nine patients this increase was present at least three months after operation. For these nine patients the mean follow-up time was nine months. It is worth noting that this group contains all those patients who had a standard leucotomy on at least one side. Neither of the two patients subjected to cingulectomy showed a persisting change, and one of these (M. D.), who was studied fairly thoroughly (three sessions pre-operatively and five post-operatively), was the only subject who showed no post-operative rise in the expectancy ratio.

In Fig. 3 these results are shown graphically. The presentation is the same as that adopted for the pain tolerance ratios in Fig. 2. The line A′ is again that about which the observations would lie if the post-operative findings did not differ significantly from those found pre-operatively. In fact, the post-operative ratios (with one exception) are all higher than those found pre-operatively.

In Fig. 3 the mean relationship between the post-operative and the pre-operative expectancy ratios is expressed by the line B′ which has the form

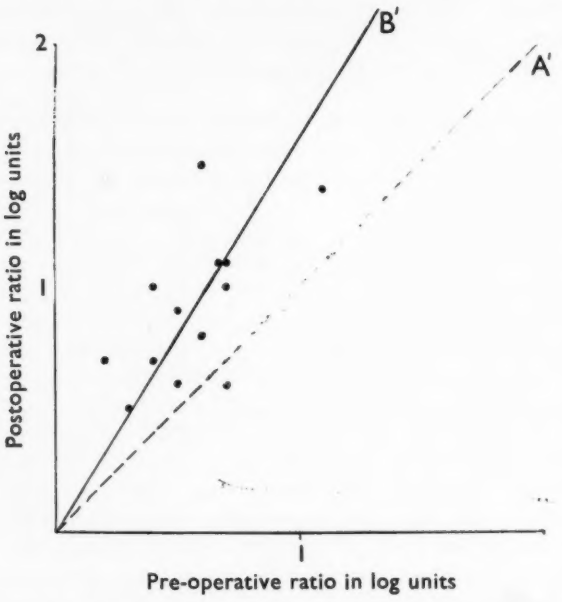

FIG. 3.—The observed relationship between the post-operative expectancy ratio and that found pre-operatively is represented by the line B′ which has the form $\log y = 1{\cdot}5 \log x$. This is significantly different ($p<0{\cdot}001$) from line A′ which represents no change.

$\log y = 1{\cdot}5 \log x$. Student's "t" test shows that this effect is highly significant ($t = 5{\cdot}40$ $n = 12$, $p<0{\cdot}001$).

It can be shown that this effect is related to the operation and is not merely the result of repetition of the test since the effect is in the opposite direction to the observed effect of practice. Ten of these 13 patients were tested more than once pre-operatively and eight showed on retesting a fall in the expectancy ratio. In one subject (A. K.) there was a rise in the ratio between the first and second and between the second and third pre-operative sessions, and the remaining patient (J. H.) showed a fall followed by a rise. These two patients both had an endogenous depressive element to their illnesses. Thus the results obtained with these patients clearly show that after leucotomy there is a reduction in the autonomic disturbance ("reflex sweating") which follows the threat of a painful stimulus as compared with the autonomic disturbance which follows the painful stimulus itself. This result cannot be explained as a practice or acclimatization effect and is not due to any alteration in the perception of, or toleration of, avoidable pain.

Individual Results.—As explained above, the effect of repeating the situation was to produce a reduction in the expectancy ratio. This effect was the opposite to the effect of leucotomy and so may partly mask the effect of the operation. Indeed, this tendency for the light response to increase with repetition of the test was so marked that repeated testing in the immediate post-operative period reduced the expectancy ratio of seven subjects to a value less than that found at the first pre-operative session. This increase in the relative response to the light signal was observed in all subjects who were tested repeatedly at short intervals and occurred even when the patient was euphoric and clearly undisturbed by the light signal. This excessive "recovery" of responsiveness to the light signal disappeared after the patient's discharge from hospital when intervals between tests increased. This observation provides additional evidence for the association of the increment in response to light with frequency of testing.

The following protocol for one patient illustrates a typical sequence of events. This patient has been chosen partly because clinically he had a successful leucotomy which altered his reaction to his own neuralgic pains, partly because the operation produced a mild but typically frontal type of personality change without definite intellectual loss, and partly because our own data are particularly complete.

Patient H. W. (Hospital No. 25598), was a married man aged 56, a painter and decorator by trade. The diagnosis was post-herpetic neuralgia and reactive depression. His main complaint was of terrible pain in the chest and back following an attack of shingles 18 months before. There was no family history of nervous or mental disease.

As a child he suffered from frequent minor ailments and had always been hypochondriacal. He has been described as meticulous, dogged and of rather restricted interests. At work he was inclined to shirk unless given a specific job to do in which case he worked well. His wife, who was said to be repeatedly unfaithful, left him and he made a somewhat histrionic attempt at suicide. He has since had no inclination to remarry.

He had suffered from urinary stone, and at the age of 28 had a chest cold which left him with a pain which has persisted ever since. In 1941 he was discharged from the army with a diagnosis of psychoneurosis. Two years later he had an illness which was characterized by nervousness, tremulousness, and a fear of heights. For the five years preceding his present illness he had remained well.

In May, 1949, he had an attack of shingles in the region of the intercostal spaces D.6–9 and this left him with pain in the left chest, which had been present ever since; it varied in severity but nothing relieved

it. After six months he managed to return to work but six months later he again had to give up and had not worked since. In addition to the pain he was tremulous and felt generally frightened and stated that he had lost all grip on himself. His appetite was poor, he lost weight, and he became depressed and somewhat tearful. He had palpitations, sweated easily, and had fears of dogs, traffic, and cancer. On examination he did not seem to be grossly depressed and stated that while in hospital his pain did not really worry him, although it was constantly present, as a dull ache. Outside he found the pain distracting when he had to do anything. There was no evidence of any intellectual deterioration. His blood pressure was 246/130 mm. Hg. On November 8, 1950, bilateral blind rostral leucotomy was performed.

Two days after the operation the patient was found to be somewhat confused, disorientated, and drowsy. There were no neurological signs. It was thought that he had had a secondary haemorrhage or thrombosis but he rapidly improved and subsequently made a good recovery. Incontinence occurred only in the first post-operative month. Although he still complained occasionally of pain he seemed little distressed and was much more cheerful in mood. He showed some definite post-operative apathy and was mildly irritable when harried.

He returned to live with the family with whom he had lodged for 20 years. At first they noted that he was much quieter, took less interest in the family, and had difficulty in getting up early in the morning. There was also an exacerbation of his usual sarcasm. He never spontaneously complained of pain. Two and a half years after the operation his landlady reported that he was a picture of health, never complained of pain, and did not appear to be anxious or depressed. He worked well and had regained his old interests but was still rather more selfish and irritable than pre-operatively. The patient was very glad that he had had the operation, and said that it had reduced the pain which nevertheless was still with him in the evenings. He was no longer tremulous, did not suffer from palpitations, and had lost his fear of cancer and traffic although he was still nervous of dogs. He expressed himself as still mildly depressed but nevertheless looked cheerful. His manner was somewhat dull and lifeless but he was able to give a reasonable summary of current events, which showed an interest and a grasp that were above average for his occupation.

Psychological Tests

Pre-operative psychological tests showed an I.Q. of 120. Two years post-operatively his I.Q. on the same tests was 125 and analysis of the scores on sub-tests suggested only minimal intellectual loss.

Table II gives the summarized data for each of the 10 occasions on which this patient was tested. Figs. 4a–d show graphically the individual responses on four of these occasions ; (a) immediately pre-operatively, (b) immediately post-operatively (20 days), (c) immediately before discharge from hospital (58 days post-operatively), and (d) on the last follow-up examination (343 days post-operatively). In these histograms the sizes of the paired responses to the light and to the shock are represented by the height of the blocked and hatched columns respectively. Fig. 4a is typical of the results obtained pre-operatively with anxious subjects. The responses to the light are relatively large but

TABLE II

RESPONSES OF H. W. TO PSYCHOLOGICAL TESTS

Session Number	Time in Days before and after Operation	Time since Previous Test in Days	London Temperature in °F.	Initial Skin Resistance in Ohms × 10^3	Initial Skin Temperature in °C.	Pain Tolerance Ratio	Mean Response to Warning Light in Ohms × 10^3	Mean Response to Shock Stimulus in Ohms × 10^3	No. of Stimulus (N)	Shock/ Light Ratio	Mean Final Light Response (N = 4)
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
1	− 5	—	49·0	89	23·2	3·7	0·56	2·62	19	4·7	0·03
2	− 1	4	48·2	161	24·6	2·7	1·72	6·27	23	3·7	0·03
Bilateral rostral leucotomy											
3	+ 20	21	57·0	253	23·1	(>2·8)	0·22	11·28	31	52·2	0·04
4	+ 30	10	45·2	195	31·0	4·0	1·12	15·49	24	13·8	0·00
5	+ 42	12	37·7	167	26·2	3·8	1·54	5·30	21	3·5	1·9
6	+ 58	16	51·2	144	33·0	3·5	4·04	7·85	25	1·9	0·90
7	+154	96	47·4	230	26·3	4·4	0·34	5·74	28	16·9	0·00
8	+210	56	69·8	270	36·7	3·3	0·17	6·21	23	37·6	0·08
9	+287	77	64·0	292	35·4	3·7	0·04	6·39	25	145·3	0·00
10	+343	57	56·8	294	31·5	(>4·1)	0·36	7·06	29	19·7	0·00

the size of the light response, and even the size of the shock response, does not appear to depend very closely on the strength of the shock. This record also demonstrates clearly that this test cannot be regarded simply as a conditioning situation because the response to the light disappears as soon as the subject is told that there will be no more shocks.

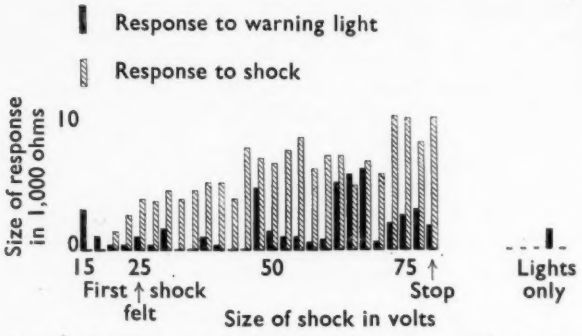

FIG. 4a.—Responses to warning lights and shocks in subject H. W. one day pre-operatively.

Fig. 4b shows the responses obtained three weeks later, 20 days after a successful modified leucotomy. The light responses have practically disappeared whilst the responses to the shocks are much increased. Two further points are worth noting: first that the shock response bears a much more direct relationship to the strength of the stimulus and secondly that, although there is a great reduction in the anticipatory response that accompanies the light, there is also a relatively marked failure to inhibit this response when the light no longer signals a subsequent shock. In Fig. 4c the responses to the light are large, but despite this, and despite the irregular size of the responses to the shock, the patient showed no signs of anxiety and indeed was rather apathetic. The presence of relatively large responses to the exhibition of the light after the electrical stimuli had ceased suggests again that there may be some failure of inhibition and perhaps some conditioning. These points are discussed more fully below.

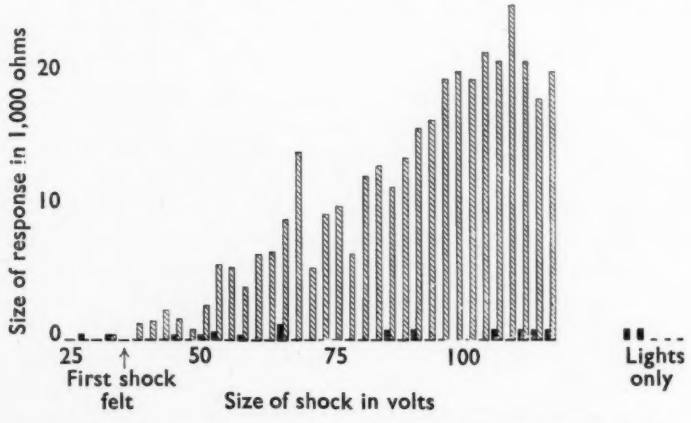

FIG. 4b.—Responses to warning lights and shocks in subject H. W. 20 days post-operatively.

Fig. 4d shows the response obtained 11 months post-operatively; the responses to the light are almost absent although there is still considerable variation in the size of the shock responses. Two anomalous light responses call for explanation. First that which occurred immediately preceding

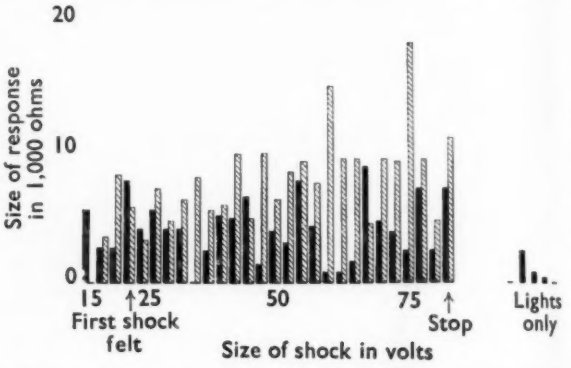

FIG. 4c.—Responses to warning lights and shocks in subject H. W. 58 days post-operatively.

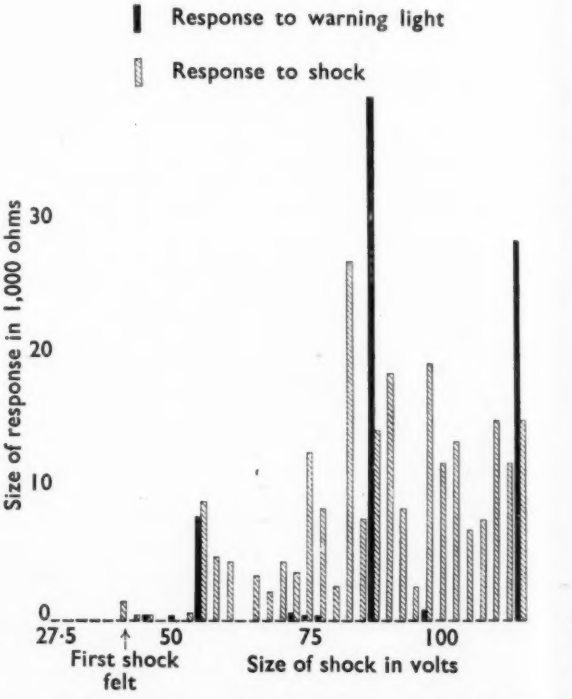

FIG. 4d.—Responses to warning lights and shocks in subject H. W. 343 d post-operatively.

the 82·5 v. shock stimulus was closely associated with a large inspiratory sigh and the fall in skin resistance is clearly a physiological response to this respiratory excursion rather than a psychological response to the warning light. Secondly this was the last session on which this patient was to be tested and, since he showed virtually no response to the warning light, it was thought that it would be as well to show clearly that this was not due purely to an overall failure to respond to psychological stimuli. Accordingly, before the last electrical stimulus, he was shown a white light instead of a red one. This resulted in a large psychogalvanic response. This response and the response associated with the large inspiratory sigh show convincingly that the poverty of the responses to the red light was not due to an overall reduction in autonomic reactivity.

Table II shows the relationship of these changes in anticipatory responses both to the operation and to the frequency of test repetition.

Discussion

Several workers have reported the effect of various psychosurgical procedures on the perception of pain. They have shown that there may be in individual cases a rise in pressure pain tolerance (Le Beau, 1950), no alteration in heat pain perception (Wolff, 1950; King and Clausen, 1952), a decrease in heat pain perception (King, Clausen, and Scarff, 1950), and an increase in the withdrawal and wince response to painful thermal stimulation (Chapman and others, 1948). These changes in the perception of, and the response to, painful stimuli tend to disappear if the investigations are repeated after the immediate post-operative recovery period has passed (Chapman and others, 1950). These results are thus essentially in agreement with the present observations on the tolerance of a painful electrical stimulus. These show that while minor changes in pain tolerance occur they are insignificant in relation to the pre-operative variation and cannot account for the relief of suffering which leucotomy often produces. Further, the consistency of the pre- and post-operative pain tolerance ratios indicates that any changes found in the expectancy test cannot be due to variations in the amount of immediate pain tolerated post-operatively. Hardy, Wolff, and Goodell (1952) argue that the response to pain after leucotomy depends greatly on the intensity of the pain under consideration and point to clinical evidence that, although reaction to persistent mild pain is much reduced by the operation, nevertheless immediate reaction to pain of high intensity may be unchanged or increased. This observation finds a parallel in our results in the unchanged or reduced tolerance ratios and the greater discrepancies post-operatively in autonomic reactivity to low and high intensities of electrical stimulation.

Previous investigators have come to contradictory conclusions concerning the effect of leucotomy on the anticipation of painful stimuli. Thus Ashby and Bassett (1950) concluded that the psychogalvanic responses to painful stimuli showed no major uniform change following leucotomy and noted in particular that the response to "threat" was unaltered. On the other hand Malmo and Shagass (1950) demonstrated that following leucotomy patients showed an increased response to painful stimuli in that they more frequently withdrew the head from painful stimuli and gave bigger psychogalvanic responses. Moreover they suggested that reduced anticipatory tension was indicated by the observation that their patients showed post-operatively fewer finger movements and fewer neck-muscle potentials in the rest periods between stimuli. Although they did not investigate the influence of acclimatization effects the results reported by Malmo and Shagass are essentially in agreement with clinical observations and with our own findings.

The anomalous conclusions of Ashby and Bassett call for further discussion. These authors recorded the psychogalvanic responses to four unpleasant stimuli: (1) a pungent gas (NH), (2) a pinch on the ear, (3) a bright flash, and (4) a touch of cotton wool to the conjunctiva. Each stimulus was exhibited in "real" form and as a "threat" (e.g., the ammonia bottle was presented corked and uncorked). Their statistical analysis showed clearly that in different patients the operation produced opposite effects on overall reactivity—a result which agrees with the detailed data of the present experiment (not presented here) and with other observations which we have reported elsewhere (Elithorn and others, 1954b). Their analysis failed however to show any differential effect of the operation on the two types of stimulus. Re-examination of their data shows that, in conformity with our own results, five out of their six subjects showed post-operatively an increase in the ratio of the response to real stimulus/response to threat. That this failed to give a significant interaction in their analysis is probably due to the large overall variability of the responses and to the small number of patients examined. It must be pointed out also that the distinction between their two classes of stimuli is not great. The threat situation was an immediate one and contained little anticipatory

element whilst the " real " stimuli were such as might lead patients to think themselves more frightened than hurt. It is clear therefore that Ashby and Bassett's observations are not in fact discordant with our own and are essentially in agreement with our hypothesis.

So far in this discussion it has been assumed that relatively large anticipatory responses to the warning light are indicative of excessive subjective anxiety and are roughly proportional to it. To a large extent this is probably true and a subsequent study in which the relative anticipatory responses of a group of patients have been correlated with an independent psychiatric assessment of anxiety will be published at a later date. Malmo and Shagass have moreover already shown (Malmo and Shagass, 1949) that higher levels of muscle tension and more frequent " spontaneous " psychogalvanic responses are found during the resting phases between painful stimuli in anxious subjects than in normal controls. We have already said that conditioned reflex terminology cannot be strictly applied to responses to a stimulus towards which a conscious " set " can be adopted by the subject. Mowrer (1938) has taken a similar theoretical standpoint and also used the term " expectancy " to describe the set adopted by the subject in situations similar to ours. Nevertheless this theoretical position does not account for the post-operative observation that the expectancy ratio tended to fall with repetition of the test although the subject remained unanxious. A similar difficulty is provided by the tendency for the response to the warning light which occurs after the subject has been told that there will be no more shocks to be post-operatively comparatively greater than pre-operatively. It could be argued that the post-operative observations are closer than the pre-operative findings to what is observed in Pavlovian conditioning experiments. Certainly our test situation resembles those which lead to the development of " trace conditioning " in animal experiments.

In delay and trace conditioning there is a tendency for the conditioned response to become delayed with training and to move up towards the unconditioned response (inhibition of delay). Our records are not on a large enough time scale to allow us to examine in detail the time relationships of individual responses, but it is clear that delayed responses to the warning light did occur particularly with frequent repetition of the test both before and after the operation. Fig. 1 shows such a delayed response.

It would seem reasonable therefore to postulate two components to the autonomic response to the warning light : (1) a response closely correlated with subjective apprehension, which is greater in habitually anxious patients ; and (2) a " conditioned " response which is determined by the previous association of the stimulus and is largely independent of subjective feelings of anxiety. This position would allow of a reduced correlation post-operatively between the expectancy ratio and subjective anxiety and would also make it easier to understand the post-operative tendency for responses to the light to occur after the subject has been told that no shock will follow. It might be that the relief of subjective anxiety after leucotomy releases comparatively simple conditioning mechanisms from control by autonomic regulating mechanisms involved in the physiological substrate of conscious anxiety. Such a release effect might involve changes in the balance of excitation and inhibition of autonomic responses.

We have argued elsewhere (Elithorn and others, 1954a, b) on independent evidence that similar damage to frontal tissue may in one subject lead to the reduction of abnormal excitation, and in another to a decrease of pathological inhibition. It is perhaps of interest therefore to point out that our present findings might be interpreted as providing evidence that leucotomy may reduce both excitation and inhibition in the same subject. If the responses to the warning signal are partly " anxious " in origin and partly due to independent conditioning then the reduction in the response to the light when the subject is told there will be no further shocks presumably involves positive inhibition of the acquired tendency to respond to light. The immediate extinction of the responses to the light when this is no longer reinforced by the shock is very marked pre-operatively. This extinction is much reduced after leucotomy and this effect may well be due to a failure of the normal tendency to inhibit the acquired conditioned response to the light when the subject is told that no further shocks will occur. Further evidence of a reduction in inhibition post-operatively is an increase in the absolute size of the shock responses and their closer relationship to the strength of the stimulus. Post-operative decrease in excitation is of course illustrated by the comparatively smaller responses to lights when the subject is aware that they will be followed by a painful stimulus. All these effects can be seen in subject H. W.

Summary

In order to test the hypothesis that prefrontal leucotomy relieves painful conditions by reducing

the anticipatory element of fear a pain-expectancy test was devised. The relative disturbance caused by a painful shock and by a preceding warning light was estimated by measuring the ratio of the psychogalvanic responses aroused by these two stimuli. Twelve of the 13 patients examined showed post-operatively an increase in this ratio which indicates a relative reduction in the autonomic disturbance caused by the warning signal. It was shown that this reduction in the anticipatory fear associated with a painful stimulus was not due to an alteration in the perception of pain or to a reduction in the amount of pain tolerated during the test.

One subject, who had been relieved by leucotomy of a totally incapacitating preoccupation with a post-herpetic neuralgia, is reported in detail.

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INTELLECTUAL CHANGES FOLLOWING TEMPORAL LOBECTOMY FOR PSYCHOMOTOR EPILEPSY

PRELIMINARY COMMUNICATION

BY

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The principal concomitants of psychomotor epilepsy have been well described by Gibbs, Gibbs, and Fuster (1948). According to them :

> " The chief clinical manifestations of psychomotor seizures may be described as follows : The patient becomes confused and as a rule amnesic but does not usually lose consciousness. His movements appear purposeful but are poorly coordinated and his manner is frequently negativistic. In general his behaviour is that of a person acting out a bad dream. Often during the seizure there are manifestations of fear or rage with screaming and shouting. In most seizures the movements are simple, repetitive and more or less automatic."

The patients with whom the present report is concerned were selected for operation (temporal lobectomy) " upon the evidence, first clinical, then electroencephalographic, that a single dominant focus existed in the anterior part of a temporal lobe ; secondly, that the seizures had not been controlled by adequate anticonvulsant therapy" (Hill, 1953).

During the course of routine psychological testing, it was observed that some of the patients who underwent the operation showed a gross learning deficit on certain psychological tests, although their intelligence level as measured by other tests showed no decline. For this reason, a testing programme gradually developed which was aimed at clarifying the nature of this deficit and establishing its reliability. The present paper presents preliminary findings on a number of patients with respect to intellectual changes before and after the operation. Since the investigation developed gradually out of clinical requirements, not all of the patients have been given all of the tests.

Review of the Literature

The literature concerned with the effects of temporal lobectomy is relatively sparse, particularly where the operation is performed for the relief of focal epilepsy without complicating factors such as tumours. Reports on psychological changes following the operation are both infrequent and usually quite inadequate, in so far as the need for statistical tests of significance is ignored and the possible influence of various relevant factors left uncontrolled.

In the most recent work attention has been mainly confined to consideration of the effects of the operation on the number of fits the patient suffers, and the possible intellectual changes resulting from this operation have been largely ignored or discussed in very general terms. Thus, Bailey and Gibbs (1951) reported on the post-operative status of 25 cases where the disturbance was confined to one lobe. They reported that no aphasic disturbances took place, but although intelligence and other psychological tests were given, no results were reported. Green, Duisberg, and McGrath (1951) investigated pre- and post-operatively 23 patients failing to respond to systematic medical therapy and demonstrating spontaneous electroencephalographic spiking in the anterior temporal areas. Although the Wechsler Intelligence Scale was given to these patients, no results were reported.

Similar studies reporting excision of the temporal lobe for psychomotor epilepsy but without any intellectual test results are those of German (1939), Furlow (1938), Penfield and Flanigin (1950), and Obrador (1953).

So far as can be discovered, only two studies specifically report test changes following temporal lobectomy. One is by Hebb (1939), who reported on a man aged 30 with post-traumatic epilepsy, most of whose right temporal lobe was removed. He showed that, while intelligence, as measured by a standardized intelligence test (the Binet), apparently remained high after the operation, nevertheless the patient performed very poorly on certain other intellectual tasks of a non-verbal nature, and he concluded that a single over-all score (such as the Binet I.Q.) could result in misleading conclusions. This study is of

importance in so far as it indicates the danger of concluding that the patient is unimpaired following the operation if the I.Q. level is unchanged—a point which the present paper will also demonstrate.

Milner (1954) has briefly indicated the results of an unpublished study of intellectual changes following temporal lobectomy for relief of focal epilepsy caused by atrophic lesions of the cortex. She studied 25 cases submitted to the operation (13 right temporal and 12 left temporal, together with 13 frontal and parietal cases as controls). A battery of 16 tests was given pre-operatively and three weeks post-operatively. The experimental and control groups were well matched with respect to age, vocabulary, and occupational status. The temporal lobe group as a whole was inferior to the controls, both before and following the operation, on two visual tests involving complex picture material. The right temporal lobe group was inferior to the other groups on tests of spatial patterning, both visual and tactual, the deficit being present before the operation but intensified afterwards. While these results seem to be of considerable importance, it is impossible to evaluate them in the absence of published data.

Since the present paper is principally concerned to demonstrate that a gross learning deficit may exist following the operation, it is interesting to note that such a learning deficit has been reported by a number of authors. Such studies, however, suffer from two severe defects: in the first place interpretation of the results is often complicated by the existence of a tumour of the temporal lobe, while in the second place the reports are usually of a clinical nature with little or no attention paid to statistical evaluation of the results. Hence, the observations and conclusions of these authors, while affording valuable hints and leads, cannot be accepted as they stand but require confirmation by properly controlled experiments.

Thus Fox and German (1935) reported the results of temporal lobectomy in a case of a large astroblastoma in the anterior portion of the temporal lobe. They reported that " retention of auditory material was definitely inferior to that of visual experience. The patient was unable to repeat a series of more than two unrelated words or numbers ". On the other hand, " the patient appeared to be of average intelligence, and with the exception of the speech difficulty no intellectual defect resulted ". This study is unsatisfactory because no proper controls were employed in the evaluation of the results.

A similar criticism may be made of the paper by Kolodny (1928), who studied 38 cases of temporal lobe tumour and found that " in 19 patients out of the 38 in this series there was definite subjective, or subjective and objective, evidence of deterioration of memory ". However, he concluded that " probably patients with organic lesions of the brain fail to fix or register an impression rather than forget a duly registered one ", i.e., the defect was one of learning rather than retention. A similar conclusion was reached by Keschner, Bender, and Strauss (1936). In a series of 110 cases of temporal lobe tumour they found disturbances in memory and orientation in 55 cases. After a careful discussion of the various phases of " memory " they concluded that in their cases the defect lay primarily in the " impression " or learning phase. " Recent events and sensory stimuli either do not enter consciousness or, if they do enter it, do not make a psychic impression of sufficient intensity to be recalled, i.e., amnesia occurs by faulty fixation."

This brief review of the literature indicates that, while a number of interesting leads may be gained from its perusal, it is impossible to draw any definite conclusions with regard to intelligence and learning following the operation. In most instances there is simply a lack of the basic data required for such an evaluation, for example, details of test results, intervals between testing pre- and post-operatively, control of intelligence, and so on. In this connexion reference may be made to the important article by Hebb (1945). He pointed out, for instance, that it is frequently assumed (especially where unstandardized tests are used) that the task is so simple that a person of normal intelligence would have no difficulty in completing it, whereas this assumption may in fact be completely incorrect. This error is very common where only clinical estimates are made of the patient's ability following the operation, especially in cases where no pre-operative testing has been carried out. It is for this reason that the literature reviewed above must be considered inconclusive.

The Sample of Patients and Operative Technique

Results on a total of 18 patients are reported in this paper. Of these 18 patients, 12 were tested by the present authors, while the results on the remaining six were abstracted from previous clinical test results.*

Table I describes the 18 patients in terms of age, sex, location of epileptic foci, duration of fits before operation, and history of trauma.

There are 11 cases where surgery took place on the dominant hemisphere, six cases of operation on the non-dominant hemisphere, and one doubtful case. This information was abstracted from the case notes

* These six patients were tested by Miss Shelagh Cox, now senior clinical psychologist, Westminster Hospital.

TABLE I
DESCRIPTION OF PATIENTS

No.	Sex	Age	Dominant or Non-dominant Hemisphere	Duration of Fits (years)	E.E.G. Evidence	History of Trauma
1	F	43	Dominant	12	L. temporal	—
2	F	25	,,	14	L. temporal	Possibly at birth
3	M	39	,,	15	L. temporal	—
4	F	22	,,	19	L. temporal	Age 6
5	F	17	,,	7	R. temporal focus	—
6	F	20	,,	7	L. anterior temporal	—
7	M	32	,,	15	L. anterior inferior temporal	Yes. Age unknown
8	M	42	,,	5	L. temporal	—
9	M	21	Non-dominant	21	R. temporal pole	—
10	F	27	,,	9	R. anterior temporal	—
11	M	23	Dominant	3	L. temporal focus	Age 20
12	M	48	,,	8	L. temporal focus	—
13*	M	45	Non-dominant	23	R. temporal	Age 27
14*	M	45	,,	43	R. temporal	Age 2 (dubious)
15*	M	23	,,	11	R. temporal	—
16*	F	15	,,	7	R. temporal focus	—
17*	M	31	Dominant	29	L. anterior inferior temporal	—
18*	M	25	Doubtful	7	R. temporal pole; occasional L. temporal	—

*Tested by Miss Shelagh Cox.

and was therefore quite independent of the psychological test results, being based on neurological and other data.

The operative technique has been fully described by Falconer (1953).

> "Starting at the Sylvian point, the incision ran backwards through the upper part of the superior temporal convolution to the foot of the Rolandic fissure, and then it curved downwards to reach the inferior border of the temporal lobe, a little in front of Labbé's anastomotic vein. Then the incision was steadily deepened to expose above and anteriorly the insula and the upper bank of the Sylvian fissure still covered by the pial mantle of the temporal operculum and posteriorly to open the hinder part of the temporal horn. Next the white matter was divided between the lower boundary of the insula and the temporal horn, thus laying open the temporal horn with the hippocampus in its floor and the choroid plexus above this. The removal of the lobe was then completed by continuing the incision across the hinder end of the hippocampus on to its medial border, as well as along the medial border of the uncus . . . our operative removals involved between 5 cm. and 9 cm. of the length of the temporal lobe."

The Tests

At different times a large number of tests have been used in the investigation of these patients. For the purposes of this paper, however, the test results to be reported fall clearly into three groups. The tests were given with the intention of measuring clinically changes in intelligence, learning, and retention following the operation.

Tests of Intelligence.—The tests falling under this heading were :

Wechsler-Bellevue Intelligence Scale (*Wechsler*, 1944).—This is a composite intelligence test, comprising five "performance" sub-tests and six "verbal" sub-tests and yielding a performance scale I.Q., a verbal scale I.Q., and a full-scale I.Q. The information sub-test was omitted (since it is unsuitably constructed for English subjects) and replaced by the vocabulary sub-test. Form I was administered pre-operatively, Form II post-operatively.

Mill Hill Vocabulary Test (*Raven*, 1948).—This is a verbal test assessing vocabulary level, and is given in two parts : synonyms (in which the patient underlines the correct word from a choice of six words) and definitions (in which the patient writes out the meaning of the words). Form I was administered pre-operatively and Form II post-operatively.

Raven's Progressive Matrices (*Raven*, 1949).—This is a non-verbal test of intelligence. For normal subjects, the spatial factor involved in this test does not seem to affect the results and the test is therefore usually regarded as a good measure of general intelligence. It is, however, quite possible that the spatial factor would be important for the patients in the present study, especially following the operation, since some of them suffered from visual difficulties. Thus it was not possible to say beforehand whether this test would serve as a good measure of general intelligence unaffected by specific disabilities following the operation.*

The Nufferno Speed and Level Tests.—These tests are not in general use and will be briefly described.

The Level Test consists of items of increasing levels of difficulty (determined empirically) made up of series of letters followed by a dot. The subject's task is to discover the principle involved in each series and supply the missing letter. Thus in the series : A A B B C C D . the missing item would be D. Ample time is allowed the subject, who is instructed to work at his own speed. The same form was used for test-retest.

The Speed Test consists of a similar series of items, of a very much simpler nature, however, such that most subjects find the task well within their capabilities. The test can be given in two forms : unstressed (where the subject is allowed to work at his own pace) and stressed (where he is instructed to work as quickly as possible, the speed element being emphasized). The score on this test is the number of items correctly completed. Equivalent forms are available for both stressed and unstressed versions of the test.

* For the Mill Hill and Matrices tests the raw scores were transformed into equivalent I.Q.s (with a mean of 100 and S.D. of 16) in order to be more readily comparable with results on the other tests of intelligence.

Tests of **Learning and Retention.**—The process of "memory" is commonly divided into three sections: the phase of acquisition of material (the "learning" phase), the phase of retention, and the phase of reproduction or recognition. This division is of course artificial since all learning involves retention. It is customary to speak about learning when a short time elapses between acquisition and reproduction, and about retention when the interval is longer. Before retention proper can be tested adequately, it is important that learning to a criterion be established in order that differences in rate of learning may be controlled.

New Word Learning and Retention Test (*Nelson*, 1953).—In this test the subject is first given a vocabulary test in the usual way (Binet is used pre-operatively, Wechsler post-operatively) until five consecutive words are failed. The subject is then required to learn the meaning of these five unfamiliar words until he has given three successful definitions—not necessarily three consecutive successful definitions. The definitions given to the subject are taken from Binet's and Wechsler's forms, and are changed at each presentation to avoid rote learning. It was known (Nelson, 1953) that normal subjects learned in five trials, i.e., required only one definition for each word in order to learn the meaning of it. Since these nouns were derived from a single testing on the Binet and in this investigation the Wechsler was used post-operatively, it was necessary to show that the Binet and Wechsler were reasonably comparable in this respect. This was done by testing six cases of temporal lobe epilepsy (not suitable for operation) on the vocabulary test of the Binet and then on the Wechsler three weeks later. Only one of these patients required more definitions (two) on retest, while one required five fewer definitions to learn to the criterion. The remainder made no errors at both sessions. Thus the Binet and Wechsler vocabulary sub-tests may be considered roughly equivalent for this type of patient.

Paired Associate Learning and Retention Test.—This test, taken from the Wechsler Memory Scale (Wechsler, 1945), involves the learning of 10 pairs of words: six easy associations, e.g., north–south, and four difficult, e.g., in–although. The examiner first presents the 10 pairs, then repeats (in a new order) the 10 initial words of each pair, the subject being required to reproduce its associate. If an error is made, it is corrected. In the Wechsler Memory Scale the procedure is repeated three times in all, giving a maximum possible score of 18 easy associations and 12 difficult ones. For the present work, a further three random presentations were constructed. The score was the number of easy and difficult associations correctly reproduced on the final trial.

Two equivalent forms of the test are available, which Stone, Girdner, and Albrecht (1946) considered to be well matched for difficulty level.

Tests of Retention.—Some attempt was made to measure retention in the following way:—

The subject was tested on the New Word Learning and Retention Test 24 hours following the learning period and was simply asked to define the five words previously given. The score was the number of words correctly defined.

Similarly the subject was given one further presentation of the Paired Associate Learning and Retention Test 24 hours following the learning period and the score on easy and hard associations noted.

A short test of memory for recent and remote events was added, consisting of a list of questions related to the past life and recent history of the patient.

The pre-operative testing was carried out about two to seven days before the operation. Post-operative testing took place 21 to 28 days following the operation. In some instances further testing has been carried out 12 months after the operation.

Results

Intelligence Tests: Pre-operative Level.—For the patients tested before operation on the Wechsler, the mean full-scale Wechsler I.Q. was 97·72 (range 67–120, 18 cases).* This value compares well with recent findings on epileptics living outside institutions whose mean I.Q. has been shown to be about the same as the mean I.Q. of a sample from the general population (Collins, 1951; Folsom, 1953). The pre-operative findings on the verbal and non-verbal tests may be compared with those of Rey, Pond, and Evans (1949), who found that their epileptoid and epileptic patients tended to score lower on the verbal when compared with the performance scale of the Wechsler and to score lower on the Mill Hill Vocabulary Scale than on Raven's Matrices. For the present group, the mean performance scale I.Q. for 16 cases was 97·88, while the mean verbal scale I.Q. was 94·38. For 11 cases, the mean Matrices I.Q. was 96·73 and the mean Mill Hill I.Q. 88·00. Although both differences are in the same direction as those found by Rey, Pond, and Evans, neither reaches statistical significance. On the Wechsler, a number of large differences in the opposite direction were observed; on the Mill Hill and Matrices, the Mill Hill score was considerably larger than that on the Matrices in only one case. On the whole, therefore, the present group of subjects may be considered substantially similar to the epileptoid and epileptic patients described by Rey, Pond, and Evans.

Intelligence Tests: Post-operative Level.—Intelligence was tested by the following:

Wechsler Intelligence Scale.—Comparisons were available for nine dominant hemisphere cases. The post-operative changes are shown in Table II. The mean full-scale I.Q. fell from 92·67 to 84·44, the difference being significant at the 0·05 level ($t = 2·218$); the mean performance scale I.Q. fell from

* In two cases the Wechsler full-scale I.Q. was calculated *pro rata* on the basis of three sub-tests.

TABLE II
RESULTS ON WECHSLER INTELLIGENCE SCALE

Subject	Performance Scale		Verbal Scale		Full Scale	
	Pre	Post	Pre	Post	Pre	Post
Dominant						
1	99	102	104	104	101	103
2	81	56	101	69	91	60
3	121	108	102	95	112	100
4	72	67	69	74	67	68
5	78	78	76	76	74	72
6	84	63	77	70	79	64
7	124	117	104	102	115	110
8	123	104	107	96	116	101
17	74	84	86	82	79	82
Means ..	95·11	86·56	91·78	85·33	92·67	84·44
Non-dominant						
9	100	96	87	87	93	91
10	126	116	113	113	120	115
13	115	107	108	103	112	106
14	105	104	99	91	102	96
16	74	87	87	93	79	89
Means ..	104·00	102·00	98·80	98·60	101·20	99·40

95·11 to 86·56, the difference being significant at the 0·05 level (t = 2·170); the mean verbal scale I.Q. fell from 91·78 to 85·33, the difference not quite attaining significance (t = 1·809). Inspection of the changes in Table II shows that some of the differences following operation can be accounted for in terms of the very poor performance of a few patients following the operation. In these instances the fall can be explained on the grounds of specific visual and/or verbal difficulties which were not present before the operation. Thus, on the performance scale, these patients complained of the difficulty of perceiving small details and had to turn their heads sideways or cover one eye to see clearly. The one patient who showed a severe drop on the verbal scale (No. 2) suffered from severe expressive aphasia following operation.

When the changes on sub-test scores for these dominant cases were examined (Table III) it was

TABLE III
MEAN CHANGE IN WEIGHTED SCORE AFTER OPERATION ON 10 SUB-TESTS OF WECHSLER INTELLIGENCE SCALE

Sub-test	Dominant (N=9)	Non-dominant (N=3)
1. Comprehension	−1·89	−0·67
2. Arithmetic	−1·11	−3·00
3. Digit span	−0·89	+0·67
4. Similarities	−1·11	−0·67
5. Vocabulary	−1·00	+0·67
6. Picture arrangement	−1·78	+0·67
7. Picture completion	−0·89	+1·00
8. Block design	−0·89	−2·00
9. Object assembly	−1·00	−0·33
10. Digit symbol	−1·22	−3·33

seen that, for all 10 sub-tests, the mean change in weighted score was negative, i.e., there was a slight but very consistent tendency for these patients to decline on all the sub-tests of the Wechsler. It is very difficult to interpret this finding, since adequate data on changes from Form I to Form II of the Wechsler are not available. The change, for instance, may be due to differences in standardization, or it may represent a genuine small general decline in ability following the operation.

The five non-dominant cases, on the other hand, showed no significant change on the Wechsler as a group, nor were there any large individual changes. Furthermore, there was no consistent pattern of change on the sub-tests, six showing a mean decline and four a mean increase.

Thus, we may conclude that on the Wechsler the dominant cases show a significant fall in full-scale I.Q.; that in some individuals the drop may be severe; but that there appears to be a general tendency for scores to fall slightly on all sub-tests. For the non-dominant cases no such decline is apparent.

TABLE IV
RESULTS ON MATRICES AND MILL HILL VOCABULARY TESTS

Subject	Matrices		Mill Hill	
	Pre	Post	Pre	Post
Dominant				
2	86	87	91	86
3	109	109	87	89
4	81	76	82	83
5	77	84	75	76
6	79	81	82	80
7	111	112	89	86
8	118	119	90	81
11	111	117	—	—
12	100	98	—	—
Means	96·89	98·11	85·14	83·00
Non-dominant				
9	85	86	83	83
10	119	119	95	95
15	113	115	—	—
Means	105·67	106·67	89·00	89·00
Doubtful				
18	86	83	102	96
Mean of all cases	98·08	98·92	87·60	85·50

Mill Hill Vocabulary Test.—Pre- and post-operative results are available for seven dominant patients (Table IV); the respective means are 85·14 (pre-operative) and 83·00 (post-operative), the difference not being statistically significant. Both non-dominant cases obtained identical scores on test-retest. These results are similar therefore to those obtained on the Wechsler Verbal Scale I.Q. in indicating a slight fall in verbal intelligence, which might, however, be due to chance fluctuations.

Progressive Matrices.—As has been pointed out already, it was not known whether the spatial factor in this test would become prominent following the operation. However, the results for 13 subjects

(nine dominant, three non-dominant, one doubtful) indicate clearly that the intellectual level, as measured by this test, does not change as a result of temporal lobectomy. The results are shown in Table IV. The pre-operative mean for all 13 cases was 98·08, the post-operative mean 98·92, the difference not being significant. For the nine dominant cases, the pre-operative mean was 96·89, the post-operative mean 98·11, the three non-dominant cases showing no change. It was interesting to note, however, that all the dominant cases, with one exception, took longer to complete the test after the operation than before. This was probably related to the visual difficulties many of them suffered from.

Speed and Level Tests.—Results on the Level Test are available for only five dominant cases, which showed a mean decline from $+0{\cdot}10\ \sigma$ pre-operatively to $-0{\cdot}23\ \sigma$ post-operatively, the difference not being significant (Table V). In none of these cases was

TABLE V
RESULTS ON THE LEVEL AND SPEED TESTS*

Subject	Level		Unstressed Speed		Stressed Speed	
	Pre	Post	Pre	Post	Pre	Post
Dominant						
2	+0·93	−0·29	0·00	+0·09	Not given	
5	−0·75	−0·92	−0·55	−0·73	Not given	
6	−1·30	−1·30	Results unreliable			
7	+0·70	+0·44	+0·04	+0·04	+0·99	+0·60
8	+0·94	+0·94	−0·09	−0·33	+0·12	+0·26
Means ..	+0·10	−0·23	−0·15	−0·23	+0·56	+0·43
Non-dominant						
9	+0·68	+0·68	−0·26	−0·32	+0·15	+0·28
10	+1·90	+2·20	+0·56	+0·15	+1·70	+0·45
Means ..	+1·29	+1·44	+0·15	+0·09	+0·93	+0·37

*Scores are given as standard scores in relation to the standardization population of this test.

the score improved. On the Unstressed Speed Test there was a mean decline from $-0{\cdot}15\ \sigma$ to $-0{\cdot}23\ \sigma$ (four cases), individual changes being very small. Only two dominant cases were given the Stressed Speed Test. The two non-dominant cases, who were given all three tests, showed no consistent changes.

The possible effects of practice on the post-operative results have been considered. It is known that retesting on the Wechsler Intelligence Scale, using Form II, tends to lead to a slightly lower score, rather than a higher one (Gerboth, 1950), though his study was carried out on normal subjects of superior intelligence, i.e., practice effects are negligible. Eysenck (1944) has shown that the average gain in raw score points for normal persons on retest on the Matrices is 3·73, for neurotics 1·96. The mean raw score increase for the 13 cases tested pre- and post-operatively in this study was 1·00; for the nine

TABLE VI
RESULTS ON NEW WORD LEARNING AND RETENTION TEST

Subject	No. of Definitions Required to Produce Three Successful Definitions of Five Words	
	Pre	Post
Dominant		
3	14	23
4	6	11
5	14	35
6	12	56
7	7	44
8	11	79
Means	10·67	41·33
Non-dominant		
9	8	6
10	5	5
Means	6·5	5·5

dominant cases 1·29. So far as is known, no data are available showing the mean raw score change on the Mill Hill Vocabulary Test. There seems no reason, therefore, to suppose that the results reported in this paper are distorted by hidden practice effects.

Learning Tests.—The same tests were used as before operation.

New Word Learning and Retention Test.—The results on this test are shown in Table VI. Although results pre- and post-operatively are available for only six dominant patients, the results are very striking. An average of 10·67 trials was required before operation, compared with an average of 41·33 trials following it. Despite the small number of cases, the difference was statistically significant at the 0·01 level ($t = 3{\cdot}155$). All of the patients performed at a lower level following the operation, and in some patients performance was extremely poor. It must be remembered that the criterion of success-

TABLE VII
RESULTS ON PAIRED ASSOCIATES LEARNING AND RETENTION TEST

Subject	No. of Associations Correct on Final Trial			
	Easy		Difficult	
	Pre	Post	Pre	Post
Dominant				
4	6	5	4	1
5	5	5	2	0
6	6	2	1	0
7	6	4	4	0
8	5	4	4	0
12	6	5	3	0
Means ..	5·67	4·17	3·00	0·17
Non-dominant				
9	6	6	4	4
10	6	6	4	4
Means ..	6	6	4	4

ful learning was not three successive accurate definitions but three at any time during learning. There is no doubt but that the former criterion would have been an impossible one for some of the patients to reach. These results become even more striking when compared with those for the two non-dominant patients, who showed no such disability following the operation.

On this test, therefore, cases whose operation was on the dominant side all showed gross difficulty in learning following operation, but there is some evidence that such disability does not occur when the operation is on the non-dominant side. It is noteworthy that before operation the dominant cases had a significantly lower level of learning efficiency on this test compared with normal subjects, the deficit being intensified following the operation.

Paired Associates Learning and Retention Test.—Table VII shows the results on this test for six dominant cases and two non-dominant cases. With respect to difficult associations, the dominant group shows a decline from a mean of 3·00 correct responses pre-operatively on the final trial to a mean of 0·17 correct responses post-operatively, the difference being highly significant at the 0·001 level ($t = 5·896$). On the easy associations, there is a drop for these patients from a mean of 5·67 correct responses pre-operatively to a mean of 4·17 correct responses post-operatively, this difference being significant at the 0·03 level ($t = 2·680$). Five of the six dominant patients were completely unable to learn difficult associations following the operation. One other patient (No. 11), who was not given this test pre-operatively, was equally unable to learn difficult associations following the operation, obtaining 11 out of 18 easy associations correct, but only one out of 12 difficult associations. (His pre-operative I.Q. was above average.) Neither of the two non-dominant cases showed any decline on easy or difficult associations following the operation. The results of these two tests, therefore, indicate that a marked deficit in the learning of verbal associations may occur as a result of temporal lobectomy. The learning deficit applies both to new and unfamiliar material and to easy associations, and seems to be particularly evident when the operation is performed on the dominant hemisphere.

The qualitative behaviour of some of those patients who dropped sharply on the Learning Test was strikingly different from what it was before operation. After operation they appeared baffled and frustrated by the Paired Associates Test and did not show any idea of how to cope efficiently with the material. They might seize on a single word and repeat it each time until eventually a correct response was obtained by chance. The performances were marked by a trial and error approach and perseveration was common. On the other hand one patient who learned easy associations without undue difficulty after the operation seemed simply unable to learn the difficult associations but did not become ruffled or annoyed; rather he did not seem aware of the drop in performance. Other patients were very much aware of their deficit and became increasingly upset by it.

Retention Test.—Since learning was not carried out to a wholly acceptable criterion, the results on the Retention Test should be regarded with caution. Table VIII shows the results on the New Word Learning and Retention Test 24 hours after original learning.* In spite of the small number of subjects, the difference between pre- and post-operative retention is significant at the 0·001 level ($t = 4·255$) for the dominant cases. Neither of the two non-dominant cases showed any defect after 24 hours.

TABLE VIII
RETENTION AFTER 24 HOURS

Subject	New Word Learning and Retention Test	
	Pre	Post
Dominant		
3	5	1
4	5	3
5	3	3
6	2	1
7	5	2
8	4	1
Means	4·00	1·83
Non-dominant		
9	5	5
10	5	5
Means	5	5

Retest After One Year

To date it has been possible to retest four of the original patients at longer intervals following the operation. The results of such testing are shown in Table IX. The results of these patients will be considered separately. They are all dominant cases.

Patient No. 3, who showed a drop of 13 points on the performance scale of the Wechsler three weeks after operation, had recovered to his former level after one year. On the New Word Learning and Retention Test, however, he required 26 definitions after one year, compared with 14 pre-operatively and 23 three weeks post-operatively, i.e., his learning ability was still impaired.

* Results for the Paired Associates Test are not shown, since most of the dominant cases failed to attain perfect learning at the end of six trials following the operation. Hence their pre- and post-operative retention scores were not comparable. Results are also not shown for the third retention measure since it was not quantified.

Patient No. 4 showed no changes in intelligence as estimated by the Wechsler three weeks and one year post-operatively, but required 14 definitions after one year compared with six pre-operatively and 11 post-operatively, i.e., her learning was still impaired.

Patient No. 11 showed a progressive increase in the Matrices I.Q. three weeks and three months post-operatively (probably a practice effect), but

TABLE IX
RESULTS ON RETEST AFTER 12 MONTHS

Wechsler

Subject	Performance Scale			Verbal Scale			Full Scale		
	Pre	3 wk. Post	12 m. Post	Pre	3 wk. Post	12 m. Post	Pre	3 wk. Post	12 m. Post
3	121	108	121	102	95	101	112	100	111
4	72	67	76	69	74	66	67	68	68
12	—	—	99	—	—	101	112*	107*	99

Matrices and Mill Hill

Subject	Matrices				Mill Hill		
	Pre	3 wk. Post	3 m. Post	12 m. Post	Pre	3 wk. Post	12 m. Post
3	109	109	—	—	87	89	—
4	81	76	—	81	82	83	81
11	111	117	126	—	—	—	—
12	100	98	—	—	—	—	—

New Word Learning and Retention Test

Subject	Number of Definitions Required		
	Pre	3 wk. Post	12 m. Post
3	14	23	26
4	6	11	14

Paired Associates Learning and Retention Test

Subject	Number of Correct Associations on Final Trial							
	Easy (maximum 6)				Difficult (maximum 4)			
	Pre	3 wk Post	3 m. Post	12 m. Post	Pre	3 wk. Post	3 m. Post	12 m. Post
11	—	3	3	2	—	0	0	1
12	6	5	—	6	4	0	—	1

*Indicates that the full-scale I.Q. was based on the results of three sub-tests only.

was entirely unable to learn difficult associations 12 months after the operation although he was in fact at this time being given a form he had already attempted before. His solitary success on this task was due to chance, i.e., he repeated the same association each time in the series until the correct antecedent presented itself. Thus he exhibited a striking learning deficit a full year after the operation.

Patient No. 12 showed no change in intelligence following the operation or after an interval of a year. This patient achieved some success with difficult associations before the operation, but was completely unsuccessful after the operation although the original series was being used after 12 months. He too showed a gross learning deficit.

Thus it is clear that four patients tested one year after the operation, although showing no deficit on the standard intelligence tests, were uniformly incapable of learning unfamiliar verbal-auditory material. This defect was the more striking in that two of the four patients were attempting to deal with material which was identical with that which had been presented to them before operation and which they had at that stage evinced less or no difficulty in learning.

Discussion and Conclusions

The conclusions to be drawn from the above investigations must necessarily be considered to be tentative in view of the small numbers of patients involved.

Changes in Intellectual Status.—The results obtained on the Wechsler, Matrices, and Mill Hill tests suggest that for the dominant cases there may be a slight general decrease in scores on intelligence measures making use of verbal or performance material, but that such a decline is not manifested on the Raven's Matrices Test. The possible long-term effects of the operation are of course unknown. For the non-dominant cases the operation appears to have no immediate effect on intellectual functioning. Some dominant cases do show large drops on the Wechsler, and these would seem to be due to specific disabilities, since these patients show no such drop on the Matrices, and such defects, when they occur, are probably temporary. One patient showing such a decline after the operation had recovered to his former level when tested a year later.

Learning Ability.—There is evidence that a severe impairment of the ability to learn new associations or the meaning of new words is a usual sequel to the operation. This impairment is found in the learning of both simple and complex material.

There is evidence that the learning impairment takes place when the operation is carried out on the dominant hemisphere, but does not result when the operation is on the non-dominant side. While the former case seems well established, the evidence for the latter is only suggestive and further study is essential.

There is some evidence that the learning impairment present after the operation may persist to the

same degree of severity at least one year following the operation. All four cases so far tested one year after operation have shown no improvement in this respect.

There is no evidence that the learning tasks are too difficult for the patients, since they served as their own controls before the operation.

There is no evidence to show that failure to learn following the operation is correlated with intelligence level as measured by the Matrices Test. For the dominant cases, rank order correlations between scores on the New Word Learning and Retention Test and measures of intelligence (Wechsler full-scale I.Q. or Matrices I.Q.) yielded insignificant values of ρ both before and after the operation.

There is a small amount of evidence that retention may be impaired following the operation on the dominant side, but the numbers involved are very small and learning to a satisfactory criterion was not established.

The possibility arises of course that the ability to learn on the New Word Learning Test was affected by the fact that most of the dominant cases were suffering from aphasic difficulties following the operation. Three points may be made in this connexion :—

In the first place, the aphasic difficulties do not account satisfactorily for the difficulties on the Paired Associates Test. On this test, the patients frequently responded with the incorrect association. If aphasic difficulties alone were operating, the patient would be unable to find the correct word, rather than give an incorrect one.

In the second place, of the six patients showing decline on the New Word Learning Test, four showed an increase of 1 weighted point on the Wechsler vocabulary sub-test following the operation ; one dropped by 1 point and one by 3 points. The aphasic difficulties therefore did not lead to any marked difficulty in defining known words ; the difficulty lay in learning the meaning of new words.

None of the four patients tested a year after the operation showed any but the slightest signs of aphasic difficulties ; yet all four still showed a striking deficit in learning ability.

It would of course be entirely premature to attempt to generalize from these limited findings to learning ability in other modalities. A further experimental investigation is at present being carried out in which aphasic difficulties will be controlled to determine the precise role they play in the post-operative fall in this kind of learning ability. A number of modalities will be investigated, including the visual, kinaesthetic, and auditory, using different types of material.

Summary

Testing of patients undergoing temporal lobectomy for psychomotor epilepsy suggests that following the operation :

(1) General intelligence is relatively unimpaired.

(2) Specific abilities may be impaired, at least for some time.

(3) A significant learning disability may result.

(4) The disability is strongly associated with lesions of the dominant hemisphere.

(5) The disability may still be present a year after operation.

(6) The learning disability is not a function of the level of intelligence of the patient or of intellectual changes following operation.

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VISUAL HALLUCINATIONS OF THE SELF IN ORGANIC DISEASE

BY

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There are few references to autoscopy in medical literature, and almost all recorded cases are to be found in Continental journals. Most frequently it has been noted in epileptics (Genner, 1947; and Lhermitte, 1951a, b). Sivadon (1937) describes the case of a doctor suffering from influenza who saw himself on his way to hospital; and Skvortzoff (1931) records similar visual aberrations in patients with functional disorders of the labyrinth. Nouët (1923) reported autoscopic hallucinations in a patient with a fragment of shrapnel lodged in the right temporal lobe. Hallucinations of the self have also been described in patients suffering from infectious fevers (particularly typhus), general paralysis of the insane, brain tumours, or post-traumatic cerebral lesions (Lhermitte, 1937, 1951a, b).

Three further cases of autoscopic hallucinations in association with organic lesions are presented. Those afflicted were fully aware that these visions resulted from their illness and were unreal; but whereas the first two patients were ill disposed to discuss the details of their experiences, the hallucinations of the third subject were so persistent as to provoke this sole presenting symptom.

Case Reports

Case 1 (R.I. 129664).—A male teacher aged 46 was admitted to hospital on December 19, 1952, complaining of malaise and vomiting. There was a four-day history beginning with a vague, uncomfortable feeling which lasted for 48 hours. Two days before admission he noticed the onset of a frontal headache of gradually increasing severity; at the same time he experienced nausea, and started vomiting the next day. The day before admission he was unable to pass urine, and had to be catheterized by his doctor. He felt drowsy and confused when admitted to hospital.

He was found to be an anxious, ill-looking man, with normal temperature and pulse. His pupils reacted equally to light and accommodation; there was no muscular weakness; the peripheral reflexes were completely normal, and there were no sensory abnormalities. There was, however, marked neck stiffness with a positive Kernig's sign. The optic fundi showed gross nipping of the veins, with silver wiring of the arteries: there was some retinal exudate but no haemorrhage or papilloedema. The pulse was regular; blood pressure 210/140 mm. Hg; the apex beat was to be felt in the fifth intercostal space 5½ in. (14 cm.) to the left of the midline, and there was a blowing apical systolic murmur. There was gross albuminuria.

Lumbar puncture on the day of admission showed a blood-stained, xanthochromic fluid. The serum and cerebrospinal fluid Wassermann reactions were negative. Two days after admission the blood urea level was 84 mg. per 100 ml.; the kidneys could concentrate to a specific gravity of 1·024.

With complete rest in bed, the patient gradually recovered from his drowsiness and confusion. Further lumbar puncture confirmed the diagnosis of subarachnoid haemorrhage complicating malignant hypertension. During his stay in hospital he was given a subcutaneous injection of hexamethonium bromide, which caused a mass incontinence and was not repeated. Hexamethonium bromide, 500 mg. twice daily by mouth, was started and this had a good symptomatic effect. On discharge the patient had no headaches, and felt quite fit in himself; there was no sign of central nervous system disease.

On further questioning as to the exact nature of the start of his trouble (earlier he had said only that he "felt ill"), he confessed to having seen an image of himself. This was the first symptom of the present trouble and, indeed, was the only symptom for the first two days. His "double" persisted for the four days before his admission to hospital. It appeared quite solid as if seen in a mirror, dressed exactly as he was. It accompanied him everywhere; at meal-times it stood behind his chair and did not reappear till he had finished eating. At night it would undress and lie down on the table or couch in the next room of his flat. The double never said anything to him or made any sign, but only repeated his actions: it had a constant sad expression. It was obvious to the patient that this was all a hallucination, but nevertheless it had become sufficiently a part of himself for the patient to draw a chair up for his double when he first visited his private doctor.

He saw the double on one occasion in hospital a few days after his admission. It was in the middle of the night; he saw the image dressed in pyjamas in the

middle of the ward getting into an empty bed: the image vanished a few moments later. This was the only occasion on which the double was not carrying out exactly the same actions as himself.

The patient had had the same sort of hallucination when he had typhus fever at the age of 15. Then it had appeared on several occasions during a period of about four weeks, and would always lead him to leave his bed and take a drink. His doctor, in fact, had forbidden him to do just this. A brother of the patient had had similar hallucinations, but no details were available.

Since his discharge from hospital on January 31, 1953, it has not been possible to pursue any further investigations.

Case 2 (R.I. 163497, C.R.H. 1646).—A man aged 62 was transferred to Cowley Road Hospital, Oxford, on December 13, 1952, from the Radcliffe Infirmary, where he had been admitted on September 12, 1952, following a "stroke." He had been unable to give an account of himself: a history of amblyopia for a few hours, three weeks previously, together with severe headache for two weeks, was obtained from the relatives. Six days before admission he suffered an abrupt transient paraplegia lasting several minutes, followed by right hemiplegia on the day of admission. He was examined by Mr. Pennybacker, who diagnosed a progressive lesion in the posterior part of the left cerebral hemisphere; a burr-hole biopsy carried out by him on October 4, 1952, revealed a multicystic malignant glioma of the left posterior temporo-parietal region.

On examination the patient was found to be a well-built man of good nutrition, continent, but mentally retarded, with perseveration and memory defects. There was a right hemianopia with bilateral papilloedema, the left worse than the right. Pupils were equal but gave very poor reaction to light and accommodation. He had right lower facial weakness, also paresis of the right arm with exaggerated reflexes. The power of the left arm and leg was good. Weakness and exaggerated reflexes were found in the right leg. The plantar responses were right extensor, left flexor. Dubious hypalgesia of the right arm was found, but definite impairment of two-point discrimination in the right hand and arm. There were no other significant clinical findings.

On October 29, 1952, seven weeks after admission, the patient began to experience visual hallucinations. He first saw a number of white lights, but was not certain of the direction in which they moved. Occasionally he saw the figure of a middle-aged man "out of the corner of his eye". The image was always that of the same man, and was always seen in the right visual field, just over the supra-orbital angle. He could not recognize the man. There were no other sensory hallucinations at this time. This right-sided image became more persistent, but its features were always the same. On November 14, 1952, he was greatly agitated, as he had seen the image of himself, which was exactly "like looking in a mirror". He realized that it was a hallucination. It persisted for about one minute, during which time all his movements were reciprocated by the image. The hallucination of the man in his right visual field became more constant during the next two months. He also had further autoscopic hallucinations during this time; and, coinciding with the onset of autoscopy, the image in his right visual field always disappeared. Later the patient became irrational and had fits of persecution mania. On January 13, 1953, he became comatose, and died three days later. A post-mortem examination was carried out by Dr. Bosanquet, of the Department of Neuropathology, Radcliffe Infirmary, on January 18, 1953.

Examination of the brain showed herniation of the cortex (about 0·8 cm. deep) through dural needle tracks in both parieto-occipital regions. The left parieto-temporal area was expanded by a reddish tumour, 1·5 by 1 cm., on the inferior surface of the left temporal lobe. Coronal section revealed a tumour mass (necrotic, haemorrhagic, and cystic, the whole traversed by large vessels) occupying almost the whole of the white matter of the left occipital lobe (Fig. 1). It appeared to be a

FIG. 1.—Case 2: coronal section of the tumour in the left occipital lobe.

glioblastoma, 8 cm. in length and 4 cm. in diameter. The tumour did not involve the cortex, but there was marked anterior oedema so that the whole hemisphere was noticeably expanded. Severe cingulate herniation on the left with flattening of the anterior horn of the left ventricle was found; the posterior horn was replaced by the tumour mass. The anterior horn was slightly

dilated. On the inferior aspect of the left temporal lobe was a tumour nodule 1 cm. in diameter. It was situated 1 cm. anterior and 3 cm. lateral to the main tumour mass. There was some upward herniation of the vermis, but otherwise the brain-stem and cerebellum were natural.

Case 3 (M.R.C. No. 1030).—A man aged 57 was admitted to hospital complaining of episodes during which he "saw himself". In 1917 his right eye was destroyed by a fragment of shrapnel which passed through the orbit into the right temporal lobe of the brain, where it is still lodged. The patient has a clear recollection of sustaining the injury, but lost consciousness a few hours later: he had post-traumatic amnesia for four or five days and was in hospital for six months.

In 1922 he first began to suffer from attacks of grand mal, about which he has only a hazy recollection. Usually there is no aura; but on one occasion he did remember gazing at the leaves of a tree rustling in the wind. Gradually they began to change into "little coloured goblins" and immediately afterwards he lost consciousness. The patient has been told that during these fits (which usually occur at night) he always has convulsions, froths at the mouth, and often bites his tongue. He has had 10 to 20 such episodes in 20 years, the last occurring in 1942.

The nature of these attacks altered in 1930, when he first began to see a black spot in front of his eye. "I've seen the *x*-ray of the bit of metal in my head and it looked just like that." The scotoma lasted intermittently for some hours: afterwards he saw the figure of a man. "I was in the doctor's surgery staring into the garden. Then I saw the man about four feet away to my left. It suddenly dawned on me who it was. It was me." These hallucinations of a normal-sized mirror image of himself lasted for about 10 days. His "double" seemed solid, but there was no feeling of affinity between them.

Seven years ago the patient had another curious experience. He was alone in a wood gathering sticks. "I knew that I was alone, yet suddenly I felt surrounded by hordes of people." This feeling, which lasted intermittently for about a week, was not accompanied by any hallucination.

In January, 1954 (one month before admission), the right-sided headaches which are a sequel of his original injury became more severe and more frequent. A fortnight later he again experienced visual hallucinations, which for the first three or four days took the form of multicoloured lights. Later they became more organized, and he saw "crowds of tiny figures all the colours of the rainbow—all myself". These figures approached and then receded. He also saw stairways and other interior parts of a house. "Sometimes it was my own house, other times I couldn't recognize it." Each episode lasted two or three minutes and was preceded by a feeling of nausea. At the time of his admission these hallucinations had become almost continuous; the remissions lasted only a few minutes and even then his vision was distorted. "The house across the road was much bigger than I knew it to be; and the wireless in the corner of the room looked the most ridiculous thing you ever saw." He stressed the fact that during these latter episodes he was conscious, fully aware of his surroundings, and quite capable of carrying on a conversation.

The patient, who farms a smallholding, is teetotal and a non-smoker. His only past illnesses have been herpes zoster in 1926 and pleurisy in 1942. There is no family history of psychological illness.

Clinical examination revealed a scotoma in the upper temporal quadrant of the left visual field: other systems appeared natural.

A blood examination gave Hb 100%, W.B.C. 8,200 per c.mm., E.S.R. 3 mm. The cerebrospinal fluid contained 48 mg. protein per 100 ml., no cells, and gave a normal Lange curve. The Wassermann reaction was negative.

A radiograph of the chest was normal.

An E.E.G. showed generalized abnormality, with episodic activity slower at the posterior part of the right hemisphere.

A radiograph of the skull showed a foreign body in the right temporal lobe (Fig. 2).

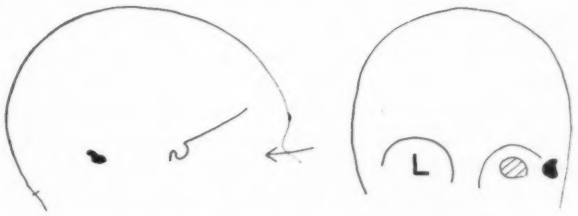

FIG. 2.—Case 3: tracings of skull radiographs showing the position of the metal fragment (black) in the right temporal lobe. This entered the skull through the right orbit.

The patient's condition immediately improved on tabs. phenobarb., gr. ¼ t.d.s. He has had no further visual hallucinations, although he occasionally gets a "funny feeling in the stomach" such as commonly precedes such episodes.

Discussion

These three cases have many contrasting features. The first patient was imaginative and highly intelligent: he was a teacher and had formerly been legal adviser to the Polish General Staff. The subarachnoid haemorrhage was probably preceded by a small vascular lesion of the brain which provoked autoscopy. This persistent autoscopic hallucination, together with a vague feeling of malaise, were the only symptoms during the first two days. Throughout the course of the illness the only localizing sign in the central nervous system was a transient meningismus.

The onset of the hallucination was sudden and without warning; it imposed on the patient's mind such a vivid conception of reality that on one

occasion he drew up a chair for his double. This strong relationship between subject and image was also noted by Lhermitte (1951a, b), who mentions instances in which the patient has tried to tap his double on the shoulder.

The second patient was a labourer of low mentality who had been employed selling firewood before admission. In this case central localizing signs were manifest long before the onset of visual hallucinations. As the tumour developed, the patient's hallucinations gradually became more frequent and more highly organized, but it was only during the terminal phase of his illness that the patient recognized the image as being that of himself.

At necropsy it was found that almost the whole of the left parieto-occipital lobe was occupied by the main tumour mass, and a small seedling was also present in the left temporal lobe. The relationship between the site of cerebral irritation and the complexity of the visual hallucinations has been the subject of much speculation : it is generally held that temporal lobe tumours give rise to more complicated and more realistic hallucinations than those of the occipital lobe. Also, the latest studies on traumatic epilepsy by Russell and Whitty show that formed hallucinations more commonly result from wounds in the posterior temporal and high parieto-occipital areas (personal communication).

The third subject also provides a contrast to the previous cases, as 13 years elapsed between injury and the first autoscopic experience. It is significant that the hallucinations were banished by sedation. Subjectively this case is similar to one of cortical atrophy described by Critchley (1953). The patient believed that he was no longer alone and imagined the "presence" to be his own self. This "bipartition fantasy", Critchley writes, "lies at the cross-roads between a temporary depersonalization, an heautoscopic hallucination and the *phénomène de sosies*."

Although there are many dissimilar features in the case histories of our three patients, yet they were in common all victims of focal brain lesions which in two of them could be localized to temporal and parieto-occipital areas. But evidence showing that autoscopy can in certain cases be associated with cerebral irritation in areas which are known to evoke formed hallucinations does not in itself explain the phenomenon. Yet it is along this entirely neurological approach that an explanation has hitherto been sought. Head and Holmes (1911) have shown that the sensorimotor systems are linked with the higher centres in relation to postural attitudes. Later Schilder (1933) developed the hypothesis that the individual possesses a notion of his physical being at the boundary of consciousness. This conception that our external actions are reflected in our psycho-physiological personalities was further developed by van Bogaert (1934). It has been variously described as the "postural scheme" (Head), the "body scheme" (Schilder), the "image of the self" (van Bogaert), and the "image of the corporal body" (Lhermitte, 1951 a, b). Indeed the latter suggests that an autoscopic hallucination should be regarded as a symptom of grave organic disease.

More recently Hécaen and de Ajuriaguerra (1952) have suggested a different neurological explanation. They divide organic cerebral lesions associated with autoscopy into two groups related to the areas of the cortex which they irritate. In the first group are epilepsy and focal lesions most commonly occurring in the parieto-occipital areas : toxic-infective states with a predilection for the basal areas form the second group. These latter conditions are said to provoke autoscopic hallucinations by "vegetative influences which act through the vestibular apparatus", or by "giving rise to an anxiety state".

These strictly neurological hypotheses fail to explain fully individual variations in the degree of complexity of hallucinations in general, and the occurrence of autoscopy in particular. It has long been known that, together with cerebral irritation, such individual variants as visual memory and the degree of visual imagery constitute a peculiarly subjective undertone to hallucinosis. Francis Galton (1883) was the pioneer in investigating the degree with which people can recall past sensations and see images in the mind's eye. He observed that visual memory varied greatly. To some people it had no meaning, whereas others were able to revive an early visual experience with hallucinatory clarity. The latter he called "visualizers"; at the other extreme are the congenitally blind, who never experience visual hallucinations (Wagener, 1948).

It would seem probable that amongst the visualizers are some (more than others) who possess this faculty of seeing a spatially localized mirror image of themselves, and we believe that it is amongst these subjects that the phenomenon of autoscopy is to be found. A focal organic lesion may, as in our cases, of course, be the precipitating stimulus which either releases or facilitates the activity of the cerebral cortical area of recall, and thus presents before this corporal group of visualizers the unsubstantial shadow of themselves.

Summary

Three cases of autoscopic hallucinations occurring in focal organic disease of the brain are presented and their contrasting features discussed.

It is tentatively suggested that autoscopic hallucinations (whatever the precipitating organic focal factor) occur only amongst a group of subjects with a highly developed visual memory sense of their corporal being.

We wish to thank Dr. W. Ritchie Russell, C.B.E., and Dr. C. W. M. Whitty for their help in the preparation of this paper, and also for allowing us to publish details of a patient (Case 3) under their care. Our thanks are also due to Dr. P. C. Mallam for permission to publish details of the first case, and to Dr. L. Z. Cosin for allowing us to publish case report No. 2.

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BASILAR IMPRESSION

BY

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RADIOLOGICAL DIAGNOSIS AND INCIDENCE

The limits of normality in the level of the uppermost cervical spine relative to the base of the skull are not clearly defined.

Chamberlain (1939) stated that normally the tip of the odontoid is either not elevated above a line from the posterior end of the hard palate to the posterior margin of foramen magnum, or, if it is, not more than a millimetre or so. On the other hand, Saunders (1943) analysed the *x*-ray films taken by a standard technique (with anode-film distance of 36 in.) in 100 "normal" subjects, and "the position of the tip of the odontoid . . . was found to be 1 mm. below a line from the dorsum of the hard palate to the dorsum of the foramen magnum, with a standard deviation of 3·6 mm.". This meant that in one in five normals the odontoid tip would lie more than 2 mm. above Chamberlain's line, in one in 19 more than 5 mm. above, and in one in 64 more than 7 mm. above the line. Saunders's findings suggest that there is a wide normal variation, and that there is likely to be no precise dividing line between the normal and the abnormal. Any criterion based on Chamberlain's line in the definition of basilar impression would be an arbitrary one.

Bull (1946) raised this objection in suggesting that variation in the inclination of the atlas relative to the hard palate provided a more certain basis for recognizing the pathological case.

Garcin and Oeconomos (1953) mention another radiological criterion described by Fischgold and Metyger. In basilar impression the odontoid and lateral masses of the atlas are elevated above a line joining the tips of the mastoid processes in a normal postero-anterior *x*-ray view of the skull. This line normally passes through the occipito-atlantoid joints.

Cases described in this paper satisfy the criterion that elevation of the tip of the odontoid shall be more than 5 mm. above Chamberlain's line in a lateral radiograph of the skull taken with an anode film distance of 28 in. While it is not argued that this is necessarily the best method, it has the virtue of simplicity. The objection that the posterior margin of the foramen magnum may be difficult to recognize in a plain radiograph can be overcome by tomography. Films were considered adequate for comparison only when taken without rotation of the head, i.e., laterals with the patient "face up" in the supine position and not with the head rotated to one side, a position commonly used for straight radiography of the head.

The figure of 5 mm. has been adopted as a convenient, though quite arbitrary, dividing line in selecting cases as abnormal. On this basis, during a review of skull radiographs of all patients admitted to the South-West Regional Neurosurgical Unit over a four-year period, eight examples of basilar impression were found among 612 patients, whose radiographs of the upper cervical spine and skull were considered adequate for comparison. This incidence of approximately one in 76 among neurosurgical patients is much smaller than in Saunders's (1943) series for the same amount of elevation of the odontoid tip in normal cases. While the subject still needs review, it may be concluded that the range of normal variation is not so wide as he suggests.

Two of the cases of basilar impression had been recognized in the period under review. These were particularly gross. In one (Case 18) the whole of the body of the axis with the odontoid and most of the atlas was elevated above Chamberlain's line. In the other, the tip of the odontoid was 15 mm. above the line. In this case the whole of the anterior arch of the atlas was also above the line, its upper margin being 1 mm. higher than the odontoid tip. Greater elevation of the anterior arch of the atlas has been seen in other cases, and is a result of the tilting of the axis stressed by Bull (1946).

Six cases were diagnosed retrospectively as basilar impression as a result of the review.

Elevations of the upper edge of the anterior arch of the atlas and of the odontoid tip above Chamber-

FIG. 1.—Lateral tomogram (Case 19) showing elevation of the odontoid and anterior arch of the atlas.

FIG. 2.—Tracing of tomogram in Fig. 1, showing Chamberlain's line.

FIG. 3.—Antero-posterior tomogram (Case 19) showing elevation of the occipito-atlantoid joints and the odontoid, also fusion of C 4 and 5.

FIG. 4.—Tracing of tomogram in Fig. 3, showing bimastoid line.

lain's line in these cases were respectively 15/12, 10/10, 10/10, 9/10, 8/8, 6/6 mm. In another 13 cases diagnosed since, the corresponding measurements have been 14/16, 10/15, 15/12, 13/11, 11/10, 9/10, 8/9, 6/8, 5/8, 6/7, 6·5/6·5, 6/6, 6/7 mm.

As may be seen, the top of the anterior arch of

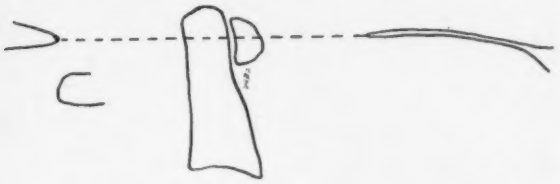

FIG. 5.—Tracing from lateral tomogram (Case 16).

the atlas was elevated to the level of the odontoid tip or above in most of these cases. In some, the whole of the anterior arch was above Chamberlain's line. This is illustrated in Figs. 1 and 2, which show the corresponding angulation of the atlas relative to Chamberlain's line. Antero-posterior views in the same case (Figs. 3 and 4) show elevation of odontoid and lateral masses of the atlas above the bimastoid line.

Fig. 5 is from a case with less elevation of the odontoid and much less tilting of the atlas. Fig. 6 from the same case shows that odontoid and lateral masses are nevertheless well above the bimastoid line.

Even if further researches show that one radiological criterion is more discriminating than another,

FIG. 6.—Tracing from antero-posterior tomogram (Case 16).

it seems likely that the distinction between normal and abnormal may still remain arbitrary. Meanwhile, the various relationships described above remain of use in a practical way in recognizing cases which may be abnormal and deserve careful study.

ASSOCIATED CONDITIONS

Basilar impression may be congenital or acquired. The acquired form is most frequently associated with Paget's disease of the skull. One example (Case 20) of this condition was seen in the present series. In another case (Case 18) the basilar impression was secondary to a local bone disease, assumed to be an osteitis, of the atlas and axis. No other case in this series was clearly acquired. A list of associated

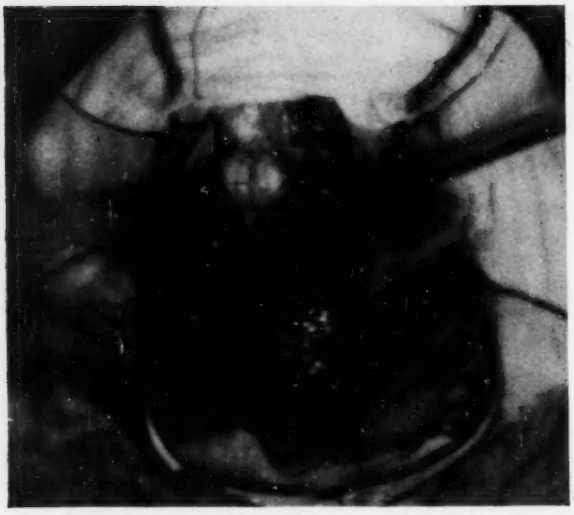

FIG. 7.—Swelling of medulla (Case 1). ? Arnold-Chiari malformation.

lesions known to be present in the cases (Table I) shows, like many other cases reported in the literature, a high incidence of developmental anomalies.

TABLE I
ASSOCIATED CONDITIONS IN 21 CASES OF BASILAR IMPRESSION

Midline cranial defect	1
Fusion of cervical vertebrae	3
Occipitalized atlas	2
Occipitalized odontoid	1
Bifid first cervical neural arch	3
Bifid first dorsal neural arch	1
Bifid first sacral neural arch	3
Sacrococcygeal sinus	1
Anencephalic child	1
Hare lip and cleft palate	1
Intracranial aneurysm	1
Dural angioma	1
Cerebellar angioma	1
? Arnold-Chiari malformation	1
Syringomyelia	1
Stenosis of aqueduct	1
Cerebellar cyst	1
? Tumour of brain-stem (unproven)	1
Osteitis deformans (Paget's disease)	1
Chronic osteitis of atlas and axis	1

Spina bifida occulta occurs in 17% of all spine radiographs according to Brain (1951), and in "every tenth man" according to Köhler (1935), but bifid arch of the atlas in unselected cases is less common than spina bifida in general. List (1941) quotes a figure of 3%.

One case of well-marked Klippel-Feil syndrome, or "brevicollis", has been seen in a boy of 7 years with, in addition to irregular fusion and wedging of vertebrae from the third cervical to the fourth thoracic level, a number of other anomalies. These included a midline cranial defect, bifid arches of the sacral vertebrae, fusion of ribs, a sacrococcygeal sinus, and a dropped shoulder (Case 8).

Fusion of two or more cervical vertebrae is discussed at length by Garcin and Oeconomos (1953), who describe it as a "minor form" of the Klippel-Feil syndrome. It was present in five of their 18 cases of basilar impression. These authors also found a high incidence of "occipitalization" or "assimilation" of the atlas (seven cases). In one (Case 1) a diagnosis of Arnold-Chiari malformation had been made at operation because of downward displacement of a swollen medulla (Fig. 7) relative to the margin of the foramen magnum, with upward inclination of the uppermost cervical nerve roots. O'Connell and Turner (1950) described this last finding in one of their cases, but did not regard it as proof of Arnold-Chiari malformation. Other authors—Gustafson and Oldberg (1940), List (1941), Lichtenstein (1942), Gardner and Goodall (1950), and Garcin and Oeconomos (1953)—describe this malformation as occurring in association with basilar impression. It is not certain, at least in the case described, whether the soft-tissue deformity was a malformation *sui generis* or secondary to the bony malformation. This patient had borne an anencephalic infant, a circumstance which might be significant. Recent statistical studies (MacMahon, Pugh, and Ingalls, 1953) confirm that anencephalus and spina bifida tend to occur in the same fraternity, and are likely to be related aetiologically.

One patient (Case 12) had an extensive syringomyelia, proved at necropsy. Lichtenstein (1943) has drawn attention to the presence of true syringomyelia as well as other forms of cavitation in the spinal cord in association with basilar impression.

The diagnosis of congenital aqueduct stenosis was made in one case (Case 3) on ventriculographic evidence, and the symptoms of hydrocephalus had been relieved by a ventriculocisternostomy, the presence of basilar impression being detected only by a subsequent review of the radiographs.

The cerebellar cyst (Case 4) was apparently a benign one, in a patient of 43 years, biopsy of its wall showing only normal cerebellar tissue.

The diagnosis of brain-stem tumour was made in another case (Case 2) on the appearance of a swollen medulla in a ventriculogram and at operation. Unfortunately a post-mortem examination was not available later.

The high incidence of the developmental anomalies (actually distributed amongst 12 cases) argues in favour of a developmental aetiology for basilar impression at least in the cases involved.

CLINICAL FINDINGS

With this selected material, no statement can be made on the incidence of neurological complications

of basilar impression in general. It is well known that most cases secondary to Paget's disease have no such complications, though the deformity is often gross. Moreton (1943), in reporting a very large series of 139 cases of basilar impression, stated that there was no absolute relationship between the amount of elevation of the odontoid and the necessity for operation. Study of individual cases in this series confirms this finding.

Six cases, with syringomyelia, stenosis of the aqueduct, cerebellar cyst, presumed brain-stem tumour, cervical spondylosis, and myxoedema, in which the clinical syndrome could be attributed at least in part to the associated lesions, have been excluded from the tabulation of symptoms and signs attributable to basilar impression alone (Tables II and III). So also have three other cases

TABLE II

SYMPTOMS OF BASILAR IMPRESSION IN 12 CASES

Occipital headache or suboccipital pain	1
Posterior cervical stiffness or discomfort	2
Vomiting	2
Loss of consciousness	3
Cranial nerve disorders	4
Unsteady gait	3
Pain, weakness, paraesthesiae, or numbness of trunk and limbs	9
Urinary incontinence	1

TABLE III

SIGNS OF BASILAR IMPRESSION IN 12 CASES

Deformity (visible, of head and/or spine)	5
Papilloedema	1
Cranial nerve palsies	5
Cerebellar signs	3
Wasting upper limbs	3
Pyramidal tract disorders	7
Sensory loss, trunk and limbs: Cutaneous	6
Sensory loss, trunk and limbs: Posterior columns	3

—one of Klippel-Feil syndrome, one of congenital intracranial aneurysm, and another of head injury —in which there were no neurological symptoms or signs attributable to the basilar impression.

Thus there are 12 cases in which the clinical syndrome could be attributed to the effects of the basilar impression alone.

The age of onset of symptoms in these cases varied from 8 to 60 years (average 45 years). Duration of symptoms when first seen varied from two months to 10 years (average two years). In the entire series the sex incidence was 12 male, 9 female.

As pointed out by O'Connell and Turner (1950) and others, symptoms and signs of neurological disorder are due to hydrocephalus, cranial nerve disorders, cerebellar dysfunction, and interference with long tracts.

In seven cases there was occipital headache or suboccipital pain. In two others there was stiffness of the neck. Discomfort was influenced by jolting (e.g., in a bus) or by change in head posture in five cases. Loss of consciousness followed headaches in three cases.

A flattened, " bun-shaped " head with a short neck was not obvious in most of these cases. Dorsal kyphosis was a prominent feature in some, with increased cervical lordosis.

Cranial nerve disorders were present in less than half the cases. Dysphagia occurred in four, aphonia in two, and trigeminal pain in two.

Cerebellar signs included nystagmus, ataxia, and unsteady gait.

Subjective complaints referred to the trunk and limbs were frequent, but varied in nature and distribution. Where present, pyramidal tract

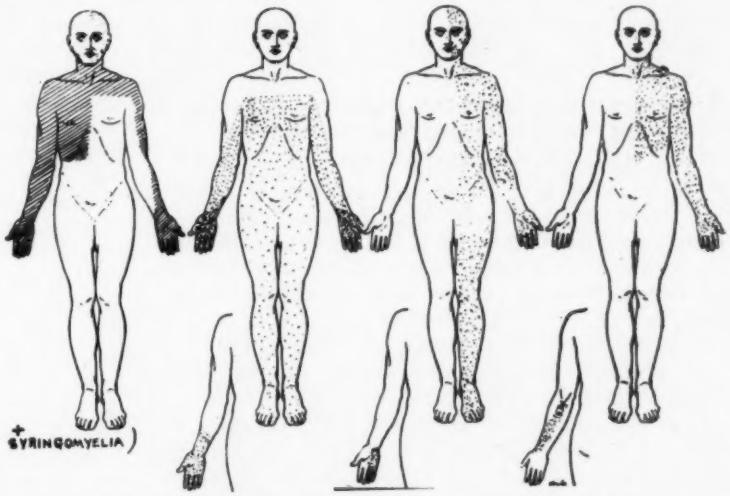

FIG. 8.—Chart of cutaneous sensory loss in basilar impression.

disorders were not of severe degree, except in one advanced case, with quadriplegia, which recovered after treatment (Case 18).

The scattered and variable nature of the signs is well illustrated by the cutaneous sensory loss (Fig. 8). The first chart, for comparison, was from the patient previously mentioned known from necropsy to have syringomyelia in addition to basilar impression. He had a typical dissociated loss, with burns on the fingers. The other charts demonstrate incomplete loss, with varied distributions. The patient with syringomyelia and three others had sensory loss also in the suboccipital region.

Cerebrospinal fluid findings varied. In the cases at present under consideration, a spinal block on jugular compression was found only once, in the most advanced case, secondary to osteitis of the atlas and axis (Case 18). In another (Case 13), with

a congenital anomaly of the atlanto-axial region and excessive mobility there, a partial block was present on flexion only. In six others tested there was no block.

The protein level in the cerebrospinal fluid was elevated to 500 mg. per 100 ml. in the case with complete block, and to 150 mg. per 100 ml. in the case with partial block. In others the protein level varied between 15 and 70 mg. per 100 ml.

Electroencephalography performed in three cases showed diffuse abnormalities. There was little change on repeated testing within three weeks of operation, but in four months post-operatively the E.E.G. was practically normal in one case and improved in another.

CASE HISTORIES

These have been grouped according to the treatment adopted. It is not implied that finality in choice of treatment has been reached in such cases.

Group 1 : Cases Diagnosed as Basilar Impression by Reviewing Radiographs after Treatment

Case 1.—G. P., a woman aged 50 years, had had symptoms for eight months. These were suboccipital headaches, vomiting, neck stiffness, papilloedema, and carpal spasms with bouts of suboccipital pain, followed by tingling in the fingers. A suboccipital decompression with laminectomy of C 1–2 was performed. The swollen medulla (Fig. 7) was displaced caudally.

The patient remained well for three years.

A review of the radiographs showed the odontoid tip 10 mm. above Chamberlain's line.

It remains uncertain whether the soft-tissue deformity here was truly an Arnold-Chiari malformation, as diagnosed at the time. Swelling or deformity of the medulla can occur secondarily to a bony malformation. Syringobulbia would be an alternative.

Case 2.—M. M., a woman aged 18 years, had had symptoms for two and a half years. These were headache, diplopia, weakness of the hands and lower limbs, facial paraesthesiae, dysarthria, and dysphagia. Papilloedema, nystagmus, a depressed corneal reflex, facial weakness, palatal palsy, weakness of the tongue, ataxia, increased deep reflexes, and extensor plantar reflexes were found on examination.

A suboccipital craniotomy, with laminectomy of C 1–2 and excision of a venous angioma of the cerebellum, was performed. The medulla was swollen.

After improvement, and relapse five months later, ventriculography showed a persistent swelling of the lower brain-stem. The patient died and there was no necropsy.

A review of the original radiographs showed the odontoid tip 8 mm. above Chamberlain's line.

The absence of post-mortem findings leaves uncertain the nature of the brain-stem lesion, whether tumour, syringobulbia, or other pathology.

Case 3.—B. R., a woman aged 27 years, had had symptoms for six years consisting of headache and tonic fits, with an olfactory aura. She had a large head. Secondary optic atrophy, bilateral ocular palsies, weakness of all limbs, spasticity of the right upper limb, and extensor plantar reflexes were found.

A ventriculocisternostomy was performed after aqueduct stenosis had been demonstrated by ventriculography.

She remained well for three years.

A review of the radiographs showed the odontoid tip 10 mm. above Chamberlain's line.

It is uncertain how much, if any, of the syndrome was attributable to basilar impression. Operative removal of the posterior margin of foramen magnum, and, in this case, the upper two cervical laminae, could have relieved this lesion incidentally in the treatment of the stenosis of the aqueduct.

Case 4.—D. L., a woman aged 43 years, had had symptoms for two years. These were occipital headache, vomiting, paraesthesiae and awkwardness of the left hand, vertigo, and blurred vision. Examination showed kyphosis, short neck, papilloedema, nystagmus, and ataxia.

A suboccipital craniotomy, with drainage of a left cerebellar cyst, was performed. No tumour was discovered. A biopsy of the wall of the cyst showed normal brain.

The craniotomy had to be reopened on two occasions in late convalescence, with laminectomy of C 1–2 and division of the underlying scar, because of persistent loculation of fluid over the posterior surface of the cerebellum.

The patient was well two years later, apart from minor symptoms. A review of the radiographs showed the odontoid tip 6 mm. above Chamberlain's line.

Recognition of the bony anomaly might in the first place have led to a wider decompression and obviated the need for reoperation.

Case 5.—J. R., a woman aged 58 years, had had symptoms for 10 years, namely pain, numbness, and paraesthesiae of the right face. She also had some occipital pain, dysphagia, transient numbness of the right hand, slurred speech, right trigeminal analgesia, absence of corneal reflex (previous alcohol injection for trigeminal neuralgia), and fasciculation of facial muscles.

The trigeminal sensory root was divided and cervical sympathectomy performed.

After initial relief the facial pain recurred. When last heard of, three years later, the patient was a voluntary inmate of a mental hospital.

A review of the radiographs showed the odontoid tip 12 mm. above Chamberlain's line, occipitalization of the atlas, and fusion of the second and third cervical vertebrae. It is suggested that in this case, in which there were confusing psychiatric features, the " atypical trigeminal neuralgia " was only part of a brain-stem disorder.

Group 2 : Cases with No Symptoms or Signs Attributable to Basilar Impression

Case 6.—A. W., a woman aged 43 years, had had fatal haemorrhage from an intracranial aneurysm.

Later review of the radiographs showed the odontoid tip 10 mm. above Chamberlain's line, and occipitalization of the atlas.

Case 7.—J. W., a man aged 43 years, received a head injury, after which a subdural hydroma was drained. He made a good recovery.

Radiographs showed the odontoid tip 8 mm. above Chamberlain's line.

Case 8.—G. E., a boy aged 7 years, was referred because of a midline cranial defect. The Klippel-Feil syndrome was seen. The odontoid tip was 7 mm. above Chamberlain's line.

Group 3 : Cases with Symptoms Subsiding without Treatment of the Basilar Impression

Case 9.—W. R., a woman aged 44 years, had had symptoms for five months, namely suboccipital pain, vomiting, blurred vision, tinnitus, vertigo, and visual hallucinations. She also had inner ear deafness. Examination showed myxoedema, with an enlarged heart and E.C.G. abnormalities.

Radiographs showed the odontoid tip 10 mm. above Chamberlain's line. The patient improved on thyroid medication, and was symptom-free 18 months later.

Case 10.—W. V., a man aged 47 years, after suboccipital pain, had a sudden unilateral palsy of the tongue, which remained, with atrophy, two months later. There was some limitation of flexion and rotation of the head.

Radiographs showed the odontoid tip 11 mm. above Chamberlain's line, and a bifid first cervical arch.

Case 11.—B. B., a man aged 22 years, had had symptoms for six months, namely headaches, vomiting, diplopia, and unsteady gait. Examination showed nystagmus, diminished corneal sensation, weakness of the left face and right palate, and bilateral spasticity of the limbs.

Radiographs showed the odontoid tip 9 mm. above Chamberlain's line.

Symptoms and most signs subsided after a lumbar puncture in hospital. He remained well six months later.

Group 4 : Cases Treated with Cervical Collars

Case 12.—A. C., a man aged 40 years, had had symptoms for six months. Two weeks after a fall, pain began at the back of the neck on jolting movements, followed by occipital headache. He had one " blackout ". He also had weakness of the right hand and paraesthesiae of the fingers. Pain in the neck on head flexion and rotation, weakness of the hands, and analgesia of the left suboccipital region and ulnar border of the right hand were found on examination.

Radiographs showed the odontoid tip 7 mm. above Chamberlain's line.

Symptoms subsided after the patient had worn a plaster collar for six weeks.

Case 13.—G. A., a man aged 38 years, had had symptoms for four months, namely pain in the shoulders, back, and legs, with paraesthesiae and weakness of the legs. Examination showed short neck, sluggish pupils, weakness of all limbs, wasting of intrinsic muscles of hands, an extensor right plantar reflex, and ataxia. Joint sense in the lower limbs was lost. The chest muscles were weak and there was slight dyspnoea. Unsteady gait had progressed till he was unable to stand unsupported. He had partial spinal block with the head flexed. The C.S.F. contained 150 mg. protein per 100 ml.

Tomographs showed the odontoid process separate from the body of the axis, and its tip fused with the basiocciput. Chamberlain's line passed through a joint between the base of the odontoid and the body of the axis. This joint allowed the skull and the atlas to move forward on the axis on head flexion.

A Minerva plaster jacket was applied for four months. Immediate improvement resulted, and the patient remained well and was at work 18 months later.

Case 14.—J. C., a man aged 59 years, had had symptoms for four months, namely pain in the left arm, weakness of both hands and lower limbs, and urinary retention. On examination, wasting of the interossei and impaired fine movements of the hands, and extensor plantar reflexes, were found.

Radiographs showed cervical spondylosis. Myelography confirmed narrowing of the spinal canal by osteophytes at the margins of the narrowed disc spaces C 3–4 and 4–5. A radiograph of the skull showed the odontoid tip 6·5 mm. above Chamberlain's line.

There was limited improvement with a plastic collar.

Immobilization was used in these three cases for various reasons. In Case 12 the syndrome was not severe ; it had followed injury (though the relationship was not certain) and the symptoms were aggravated by movement. In Case 13 the need to restrain abnormal mobility of the occipito-cervical junction was clear. Operative exploration with decompression might have further increased mobility and made a bone graft more difficult. In the event, dramatic and lasting relief followed plaster fixation. In Case 14 the collar was applied as treatment for the cervical spondylosis. A Minerva plaster collar was not tolerated. Because of a chronic chest infection, some doubt as to the exact pathogenesis of the neurological lesion, and the patient's age, no operative treatment was considered.

Group 5 : Cases Treated by Surgical Decompression

Case 15.—R. A., a man aged 20 years, had suffered from frequency and enuresis since childhood. He had to give up work as a hairdresser because of involuntary jerking of the arms. Eleven years before admission he had a total quadriplegia of a few days' duration following

a fall, then headaches, convulsions, and increasing weakness of all limbs. Nystagmus, wasting of the upper limbs, total analgesia and absence of thermal sensitivity over the upper limbs, upper trunk, and trigeminal area on one side were found. A radiograph of the skull showed a " tam-o'-shanter " deformity, and the odontoid tip was 15 mm. above Chamberlain's line.

A suboccipital decompression with laminectomy of C 1–3 was performed. A mat of adhesions was found obliterating the cisterna magna. Immediately after the end of the operation and removal of the intratracheal tube, respirations became laboured, the pulse slow and weak, the pupils fixed and dilated. The patient's condition improved with coramine, reinsertion of the tube, and oxygen.

He developed spastic flexion of both wrists and metacarpophalangeal joints (cf. Case 1), and then quadriplegia. Bronchopneumonia and meningitis followed and he died two months after operation.

Necropsy showed a true syringomyelia in addition to the basilar impression.

Case 16.—F. P., a man aged 60 years, had had symptoms for eight months. Suddenly he had felt dizzy with a rushing sensation at the back of the head, more on the left. He had several similar episodes, with constant stiffness and discomfort at the back of the neck. Examination showed weakness of the shoulder girdle, unsteady gait, hypalgesia at C2–T9 on the left side, and dorsal kyphosis. Radiographs showed the odontoid tip 8 mm. above Chamberlain's line (Fig. 5).

A suboccipital decompression with laminectomy of C 1–2 was performed.

After three weeks of good progress with improvement in symptoms and signs the patient developed resistant meningitis and died two months later of bronchopneumonia.

Necropsy showed, in addition to indentation of the lateral lobes of the cerebellum by raised lateral margins of the foramen magnum, that the lumen of the right vertebral artery was obliterated at foramen magnum level by arteriosclerosis.

Case 17.—D. K., a woman aged 41 years, had had symptoms for one year. These were attacks of suboccipital headache followed by loss of consciousness (no convulsions) and weakness of the left limbs. Examination showed slight left spastic hemiparesis and hemianalgesia. Radiographs showed the odontoid tip 10 mm. above Chamberlain's line. Ventriculography was normal.

A suboccipital craniotomy with laminectomy of C 1–2 was performed.

Symptoms and neurological signs disappeared immediately. She was well, apart from minor symptoms, over a year later.

The progress of the next two cases under treatment is described in more detail, as they illustrate clearly their peculiar problems. Case 18, at first undiagnosed, developed an acquired basilar impression to a remarkable degree, with very severe neurological signs. Treatment was prolonged, but apart from the immediate post-operative period, recovery was uninterrupted. Case 19 did not present such a formidable picture, neurologically or radiologically, but the post-operative course was stormy.

Case 18.—A man aged 53 years was first seen in November, 1949, with meningismus and some C.S.F. pleocytosis (cells 193 per c.mm., 70% polymorphs). There were subsequently some dysphagia, hoarseness, and slurring of speech, and poor movement of the palate and pharynx and pharyngeal anaesthesia. Biopsy of an enlarged cervical gland showed " reactive inflammatory hyperplasia ".

He recovered from this acute illness and returned to work, but was seen again in February, 1951. Increasing weakness of the limbs since October, 1950, had progressed rapidly almost to complete quadriplegia. There was gross wasting of the shoulder girdle and trapezii

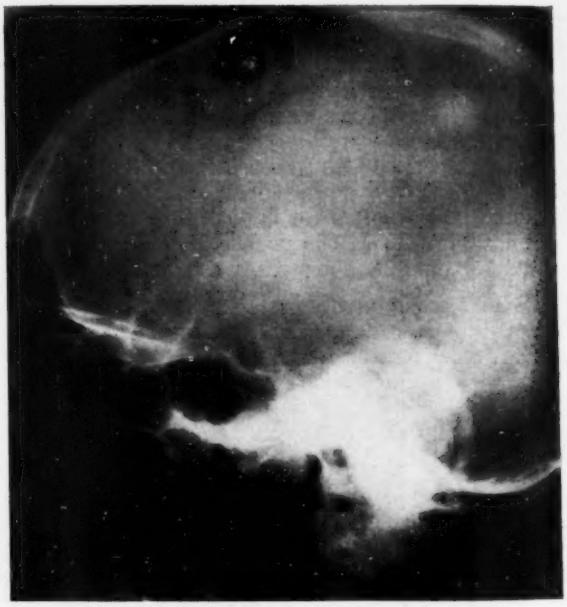

FIG. 9.—Extreme basilar impression: all of body of C2 above Chamberlain's line; retropharyngeal soft-tissue swelling (Case 18).

with severe weakness in these muscles and the sternomastoids. He had faecal and urinary incontinence. The voice was very weak. Radiographs showed gross basilar impression, i.e., the odontoid and what could be seen of most of atlas and axis were pushed upward and indeed were obscured in the lateral *x*-ray view by the mastoid air-cells (Fig. 9).

A review of the radiographs of November, 1949, showed that there was some degree of basilar impression at that time, the odontoid tip being 10 mm. above Chamberlain's line, though it had increased in degree since. Now it also appeared there was some disorganization of the odontoid and soft-tissue swelling in front of it in the post-pharyngeal region. Biopsy of this swelling showed chronic granulation tissue.

Some immediate improvement followed traction with skull callipers, and five weeks later suboccipital decompression was performed with laminectomy of C 1–2 under local anaesthesia. The medulla and uppermost cord were seen to be dorsally displaced. Skull traction was maintained during the operation and while the patient was removed from the table to a plaster shell, care being taken to avoid twisting the head.

At this stage the patient abruptly lost consciousness and respirations became very slow and periodic. Respirations improved after a dose of methedrine intravenously, and on being given a second dose, about 20 minutes after being moved from the operating table, the patient suddenly regained consciousness and respirations became normal.

Further recovery was slow but steady. The patient remained another 11 months in hospital, during which time he had a more extensive laminectomy of C 3–5 and a rib graft to the occiput and lower cervical spine. He has since made a complete neurological recovery and was well (apart from a stiff neck) and at work in July, 1954 (Fig. 10).

FIG. 10.—Extreme basilar impression : shortening of neck (Case 18).

The origin of the osteitis which may have supervened and aggravated a pre-existing basilar impression is obscure. The nasal septum was largely destroyed, and the patient had a history of treatment for syphilis, though details were lacking and the Wassermann reaction was now negative in blood and cerebrospinal fluid.

Case 19.—A man aged 37 years had had symptoms for five years, consisting of pain in the neck and left upper limb, tremor of the head and upper limbs, and giddy attacks. The odontoid tip was elevated 12 mm. above Chamberlain's line. There were asymmetry of the skull, distortion of the foramen magnum, and fusion of the fourth and fifth cervical vertebrae (Figs. 1–4).

Recent episodes of severe headache followed by unconsciousness led, after careful consideration, to a decision to operate, despite the fact that after a period of rest in hospital the patient was symptom-free and had no abnormal neurological signs apart from slight tremor and slowness of gait.

Suboccipital decompression with removal of the arch of the atlas was performed under general anaesthesia. Inversion of the margins of the foramen magnum was marked. The cerebellar tonsils were small, flattened, a little prolapsed, and very closely adherent to the lower medulla. The junction of the medulla and uppermost cervical cord was angled dorsally and rotated a little. The foramen of Magendie was obstructed by a transparent membrane through which was made an opening into the fourth ventricle.

The patient failed to recover consciousness after being moved to bed and stopping the anaesthetic. There was some fasciculation of the face on one side. The respirations were periodic with long periods of apnoea. This improved somewhat with intravenous and intramuscular coramine and oxygen, but no tone returned to the jaw muscles. Laryngoscopy was very difficult. The aditus laryngis was apposed to the posterior pharyngeal wall, which was unduly prominent because of a marked cervical lordosis. There was seen to be some unilateral fasciculation of the tongue. Finally, as the airway had been maintained only by strongly holding the jaw forward, an intratracheal tube was reinserted and oxygen administered.

Five hours after the end of the operation the patient was moving the right upper limb, and respirations were straining in character. A tracheotomy was performed. The patient remained semi-stuporose for the next two days and developed a severe chest infection requiring frequent aspiration of profuse secretion from the air passages.

Three weeks after the cranial operation, gastrostomy was performed because of difficulty with an indwelling oesophageal feeding tube, which caused local irritation in the nose and throat and did not prevent inhalation of secretions and regurgitated feeds. Daily lumbar puncture drainage had to be performed because of persistent accumulations of fluid in the suboccipital region. Over the next month his condition slowly improved and the tracheotomy and gastrostomy tubes were removed.

Seven months after operation there was still marked unsteadiness of gait, though tremor had virtually disappeared and the plantar reflexes, previously extensor, had become flexor.

Group 6 : Cases Left Untreated

Case 20.—C. P., a woman aged 58 years, had had symptoms for 18 months, namely tinnitus, pains in the head and right face, dysphagia, and "giddy turns". On examination a large head, deafness, exaggerated tendon jerks, an extensor left plantar reflex, hypalgesia of the right upper limb, and impaired joint sense were found.

Radiographs showed advanced Paget's disease of the skull, and the odontoid tip 16 mm. above Chamberlain's line.

This patient was not entirely incapacitated, despite a variety of symptoms. It was not clear that all these could be attributed to deformity of the foramen magnum.

Finally, her cardiovascular state contraindicated any but the most urgent surgery.

Case 21.—A. G., a man aged 56 years, had had symptoms for five years, namely, attacks of tonic spasm of trunk and limbs, weakness of the legs, and dysphagia. He had been bedridden for over a year. Examination showed limited ocular deviation, dysarthria, wasting of the shoulder girdle, and a spastic right hemiparesis. He was incontinent. He had a hare lip and cleft palate. The testicles were not descended.

Radiographs showed the odontoid tip 6 mm. above Chamberlain's line.

Here there was an advanced neurological syndrome with a relatively slight basilar impression. This suggested the possibility of an associated soft-tissue pathology, rather than a simple compression due to a bony anomaly. His physical state was very poor, and it was considered that any surgery would be attended by grave risk without likelihood of benefit.

TREATMENT

The results of treatment are shown in Table IV. It is clear from a study of the cases described that no routine prescription can be laid down for their handling.

TABLE IV

RESULTS OF TREATMENT IN 21 CASES OF BASILAR IMPRESSION

Well	5
Improved	3
No improvement	2
Died:	3
Of associated disease ?	1
Of post-operative complications	2
No treatment to date	8

In the first place, many cases of basilar impression (more than indicated in this selected series) show no neurological complications. Of those that do, in some the complications are of minor degree and are not progressive, or may subside, either spontaneously or with rest. Some severe cases may be unsuitable for surgery. In others, concomitant lesions may be more important, though the basilar impression may contribute to the syndrome.

In a few special cases, immobilization in a collar may be worth a trial. Even where there is not abnormal mobility, as in Case 13, stress from movement or friction at the level of the foramen magnum may play as great a part in the production of the neurological syndrome as simple compression. An analogy may be drawn with cases of cervical spondylosis. The lasting benefit from temporary immobilization in Case 13 was striking. The more adequate immobilization of the occipito-atlantal joint by a Minerva type of plaster collar (as opposed to a short collar under the chin) is worth stressing.

Traction was used in one bedridden patient (Case 18). Serial radiographs showed minimal correction of the deformity, and benefit from this treatment was attributed mainly to the immobilization procured by this method in conjunction with a plaster bed. Immobilization was a most useful first stage in treatment in this neurologically advanced case, before the major procedure of operation. Such a preliminary manœuvre might be useful in other severe cases, though no reduction of bony deformity could be expected, and it would not be likely to obviate the need for surgery.

Surgical decompression of the foramen magnum region is the logical treatment in any but minor cases, where the neurological syndrome is progressive. In view of the danger of serious complications, even in cases which do not appear neurologically advanced (Cases 16, 19), this should not be left too late. The possibility of associated soft-tissue anomalies is a hazard (Case 15), but not necessarily a fatal one (Case 1).

The decompression, as pointed out by O'Connell and Turner (1950), must be adequate. This means laminectomy of at least the upper two cervical vertebrae and division of any underlying band of fibrous tissue (Case 4). The dura mater should be opened. In addition to providing more efficient decompression, this allows access to any obstructing arachnoidal scars or membranes (Case 19). In view of the possibility of generalized compression of the posterior fossa, perhaps with upward herniation of the cerebellum and midbrain compression as postulated by several writers, a fairly wide suboccipital decompression is desirable. This is readily obtained by a classical suboccipital decompression using a transverse incision by the superior nuchal line, but not so certain with the easier midline vertical, muscle-splitting approach. Details of operation may, of course, vary in the presence of associated lesions, such as the Arnold-Chiari malformation or subarachnoid adhesions.

Gentleness in handling these patients cannot be over-emphasized. Alarming disturbances of respiration, circulation, and state of consciousness have been encountered as immediate post-operative complications (Cases 15, 18, 19). That these were not simply post-anaesthetic complications is shown by the patient who had local anaesthesia (Case 18). The susceptibility of the medulla to movement or posture of the head in such cases was illustrated by Case 1, who appeared at operation to have an Arnold-Chiari malformation. Although chart readings throughout the operation had shown no disturbance, respirations ceased when the patient was turned on her right side after having been put back to bed. They began again when she was put on her back. She was again carefully turned to the

half-right position and, after another apnoea of half a minute, respiration continued spontaneously.

The short neck and increased lordosis have caused difficulty in tracheal intubation for the anaesthetic and with the airway post-operatively, the laryngeal aditus tending to fall back against the posterior pharyngeal wall.

Bronchopneumonia was a troublesome post-operative complication. This was not surprising in view of the liability to bulbar disorder, with motor and sensory loss, and reflex disturbances of the pharynx and larynx. Moreover, some of these cases had severe kyphosis and fixation of the chest with a diminished respiratory excursion. Some had weakness of the intercostal muscles and diaphragm. There appeared to be a particular susceptibility to morphine and other narcotics. This has been observed in patients with kyphosis undergoing surgical treatment for other conditions.

In addition to the post-operative complications described above, pleocytosis in the C.S.F. developed in four cases and persisted to a degree that suggested infective meningitis. In only one of these did the fluid become frankly purulent with culture of an organism, and that very late in the course of the illness, so that there remained some doubt as to whether the organisms were not secondarily introduced. Repeated lumbar puncture in any case had to be performed over a long period because of persistent reaccumulation of fluid. (This difficulty in management has been noted by O'Connell and Turner.)

A bone graft for permanent fixation (involving permanent stiffness of the neck) may sometimes be desirable. In the one patient (Case 18) in this series in whom it was used the circumstances (destruction of the atlas, presumed to be by chronic osteitis) were unusual. In most cases it is not likely to prove necessary.

SUMMARY

The lower limit of abnormality in basilar impression appears to be arbitrary, though various radiological criteria serve to identify the well-marked case.

The incidence of this condition in neurological patients is appreciable, though less than might have been expected from the previously recorded incidence in normal subjects.

Associated skeletal and soft-tissue lesions of a developmental character have been commonly found in this series of 21 cases.

Surgical treatment has been required where a neurological syndrome has been progressive—in about half the cases. Special difficulties in management have been due to disorders of the medulla, the respiratory tract, and the cerebrospinal fluid circulation.

I must acknowledge the helpful cooperation of Dr. A. M. G. Campbell, who referred for treatment many of the cases recorded here; my thanks are also due to Dr. H. L. Hoffman, who referred others, and to Mr. G. L. Alexander, who has kindly allowed me to include in this study cases under his care.

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SOME OBSERVATIONS ON THE ELECTROENCEPHALOGRAM IN CEREBRAL TUMOURS

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The usefulness of the E.E.G. in the localization of intracranial space-occupying lesions is now generally accepted. High amplitude slow waves in cases of intracranial tumours were first observed by Berger (1931). The tumour itself is electrically inert and the slow waves arise from partially damaged surrounding tissue (Foerster and Altenburger, 1935 ; Walter, 1936 ; Scarff and Rahm, 1941).

Increased intracranial pressure can produce slow activity and there are probably at least two mechanisms. Williams (1939) clearly showed that cerebral oedema played a part by temporarily reducing the slow activity associated with cerebral tumours with intravenous hypertonic solutions ; reduction of the C.S.F. pressure by lumbar puncture, however, had no such effect. Stewart (1941), in experiments on cats, found that slow activity could be produced only when there was active internal hydrocephalus causing tension in the cerebral white matter. Acute and chronic intracranial pressure without hydrocephalus did not produce slow activity. Scarff and Rahm (1941) described two patients with increased intracranial pressure secondary to craniopharyngiomata. Large slow waves were recorded from the surface of the distended dura overlying the middle frontal convolution ; immediately following ventricular aspiration through a brain cannula, the slow waves disappeared.

A review of the records of 170 intracranial space-occupying lesions, confirmed by operation or necropsy (see Table), showed results similar to those obtained by other workers (Cobb, 1950 ; Renfrew, Cameron, and Haggar, 1953). A few cases are of interest and help to illustrate certain general principles as well as some pitfalls in interpretation. The importance of oedema in supratentorial tumours and active ventricular dilatation in infratentorial tumours in the production of slow activity is stressed.

TABLE

E.E.G. IN 128 SUPRATENTORIAL INTRACEREBRAL SPACE-OCCUPYING LESIONS, EXCLUDING THOSE NEAR THIRD VENTRICLE

Type	No.	Abnormal	Lateralized	Localized	Normal
Primary neoplasms	87	82	79	52	5
Abscesses	17	17	13	10	—
Metastases	24	22	14	6	2
Total	128	121	106	68	7

Supratentorial Tumours

Meningiomata, being slow-growing tumours, are usually considered to cause little abnormality in the E.E.G. However, two cases of basal meningiomata are reported which caused marked generalized cerebral oedema and high amplitude slow activity in the E.E.G.

Serial No. 2429.—A woman aged 48 had a meningioma of the right sphenoidal ridge. At necropsy the brain was elevated by the tumour and generally oedematous. The record was very abnormal with dominant slow activity at 2 c./s., which was chiefly frontal and right-sided. No definite focus was seen.

Serial No. 2263.—A woman aged 40 had a right olfactory groove meningioma found at operation. The first record showed dominant slow activity at 1 to 3 c./s. which was most marked on the right side. Following caffeine sodium benzoate injections, 2 ml. intramuscularly at six-hourly intervals for two days, the record was repeated. The slow activity was reduced in amount and maximal in the frontal region (Figs. 1 and 2).

The brain at necropsy in cases of cerebral metastases often shows marked oedema and this probably explains the gross generalized abnormality in the record. The oedema may spread across the midline via the commissures, especially the corpus callosum. In the early stages, however, even a secondary tumour may cause little or no abnormality. A patient with recent Jacksonian epilepsy associated with a primary bronchial carcinoma had a normal record. In another patient a small

secondary carcinoma found at necropsy in the right frontal region caused no electroencephalographic abnormality.

A normal record in cases of supratentorial tumours is usually attributed to slow growth or to the site of origin. Three cases in the series are described below :—

Serial No. 2218.—A woman aged 32 with a history of three months' headaches and two months' vomiting showed on examination early papilloedema of the left disc and a weak left arm with pseudoathetosis and sensory changes. The E.E.G. was normal. Operation revealed a glioma in the right parietal region.

Serial No. 2803.—A man aged 39 had persistent headaches for four months, three attacks of sudden weakness of the legs without loss of consciousness, and a short history of vomiting. On examination there were no abnormal physical signs. The E.E.G. was normal. Necropsy three months later revealed an extensive glioblastoma in the left parieto-occipital region spreading across the midline via the corpus callosum.

Serial No. 764.—A woman aged 35 had, in October, 1947, a major fit, in 1949 Jacksonian fits involving the left arm, and in 1950 bilateral papilloedema. The E.E.G. was normal except for a little fast activity ; no slow waves were seen. Operation revealed a right parietal astrocytoma.

It is noteworthy that not one of these tumours was a meningioma. In the following case, however, a meningioma caused minimal abnormality which can probably be attributed to the site of origin of the tumour.

Serial No. 8.—A man aged 44 had a right parasagittal meningioma at operation with one year's history of right-sided Jacksonian fits and minimal right-sided pyramidal signs. The E.E.G. showed excess theta activity at 6 to 7 c./s. in the resting record.

Theta activity is usually attributed to deep-seated lesions, but in this series was found in records of tumours at all sites. Diffuse theta activity suggests a lesion near the third ventricle (Walter and Dovey, 1944), and was found in the majority of tumours of the third ventricle, suprasellar tumours, and sellar tumours with abnormal neurological signs. But three out of five thalamic tumours caused ipsilateral delta activity.

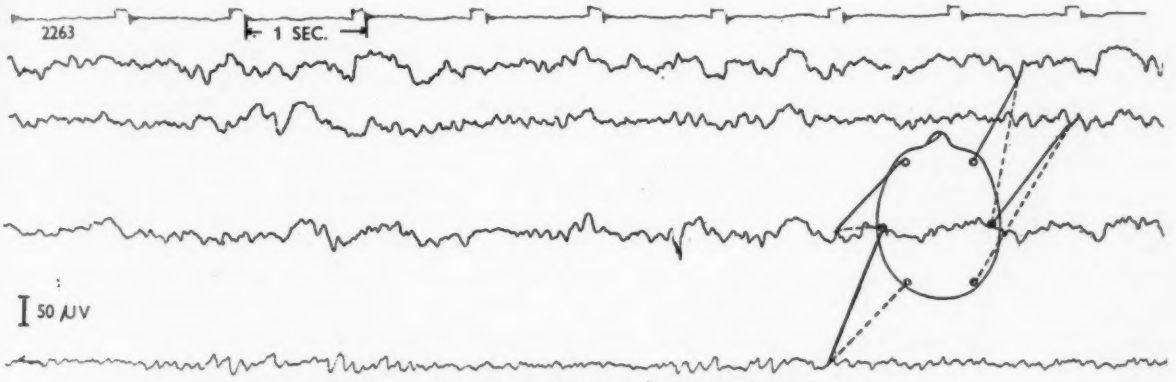

FIG. 1.—Serial No. 2263 : E.E.G. before caffeine sodium benzoate injection.

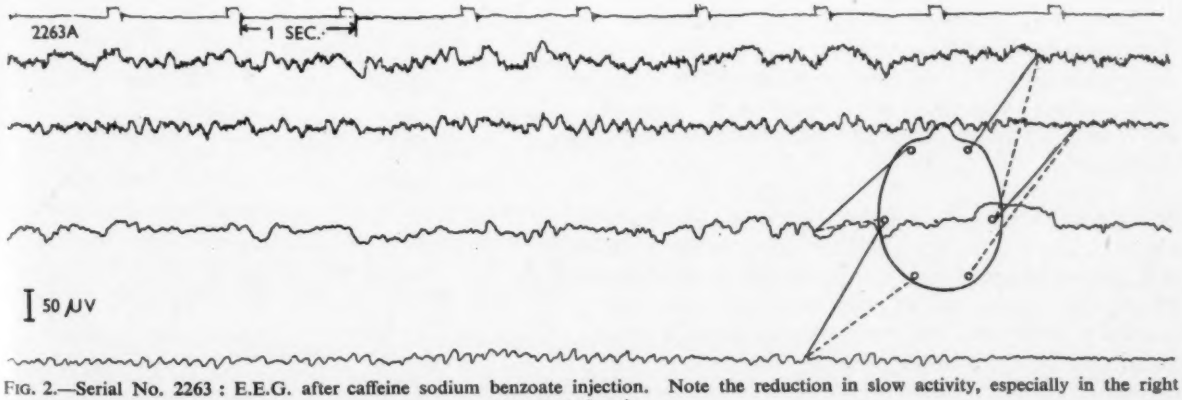

FIG. 2.—Serial No. 2263 : E.E.G. after caffeine sodium benzoate injection. Note the reduction in slow activity, especially in the right post-central region.

Infratentorial Tumours

A normal record or a generalized abnormality is the usual finding in posterior fossa tumours. However, the following case showed a focal lesion, the mechanism of which was probably localized tension on white matter :—

Serial No. 2407.—A woman aged 53 had increasing mental deterioration and a few months' history of staggering. On examination she was demented and euphoric and had bilateral papilloedema. The clinical diagnosis was a frontal lobe tumour and the E.E.G. showed bilateral frontal high amplitude slow waves, more marked and occasionally focal on the left side. Ventriculography, however, showed hydrocephalus which was most marked in the frontal horns, and operation disclosed a cerebellar haemangioblastoma.

Three cases out of a total of 21 posterior fossa tumours (cerebellar tuberculoma, recurrence of a haemangioblastoma, and a medulloblastoma) showed an abnormality in one occipito-temporal region without clinical evidence to support such a localization ; it may well be that the abnormality was due, at that time, to undue pressure on the white matter around the posterior horn. The tuberculoma was in the left cerebellar hemisphere and the electroencephalographic abnormality was right-sided. Bagchi, Lam, Kooi, and Bassett (1952) found similar contralateral changes in 25 out of 28 lesions of the cerebellar hemispheres, and this they attributed to interruption of physiological pathways. At least it seems unlikely that vascular changes due to venous obstruction or posterior cerebral artery compression could be the main factor.

The effect of caffeine sodium benzoate was tried on one patient with a cerebellar metastasis having diffuse 4 to 6 c./s. activity, with no change in the record.

Subdural Lesions

The E.E.G. in cases of subdural haematomata and hydromata is disappointing. There were five cases of subdural haematomata in the series ; two were correctly localized on the basis of reduced alpha activity on the abnormal side, one also having excess delta activity on the side of the lesion. In two cases without alpha asymmetry the delta activity was on the contralateral side. In a generally abnormal record the greater theta activity was on the side of the haematoma. In four cases of subdural hydromata one record was normal, one was generally abnormal, and two showed greater delta activity on the contralateral side. In general, the records in subdural lesions are less abnormal than in intracerebral lesions for the same level of consciousness and clinical abnormality. In two cases where there was considerable abnormality in the E.E.G. there was also evidence to suggest recent cerebral contusion. Other authors have been successful in lateralizing subdural lesions in 70 to 75% of cases (Rodin, Bickford, and Svien, 1953 : Sullivan, Abbott, and Schwab, 1951). The chief features of value are focal delta activity and reduction of the alpha rhythm on the side of the haematoma. The generalized abnormality in the record in cases with tentorial herniation is probably due to anoxia affecting the brain-stem reticular substance. Experimental lesions in the brain-stem in cats produced high amplitude slow waves (Lindsley, Bowden, and Magoun, 1949). This may be the principal mechanism producing the diffuse abnormality in subdural haematomata (Rodin and others, 1953).

Discussion

There are two main mechanical factors in the production of high amplitude slow waves at a distance from the tumour. In supratentorial lesions this would chiefly be due to cerebral oedema, and in infratentorial lesions to active dilatation of the ventricles. In the former, caffeine sodium benzoate has been found clinically to be of great benefit in the relief of headaches due to increased intracranial pressure. It is suggested that this may be due in part to reduction of cerebral oedema, possibly as a result of a diuretic action and possibly due to a change in cerebral blood flow. This drug is more easily administered and produces a more prolonged effect than do hypertonic solutions given intravenously.

Infiltrative supratentorial tumours, even when extensive, may cause so little mechanical or metabolic disturbances of normal cells that slow activity does not result. A normal record should not mislead the clinician in the presence of other strong evidence of tumour. This can be contrasted with compressing tumours such as meningiomata, abscesses, and cysts, which when actively expanding produce marked abnormality.

There is nothing original in the statement that cerebral oedema causes slow activity, but having seen many brains sectioned and compared the findings with the E.E.G. I have been impressed by the importance of this factor. The oedema need not be interstitial, and failure to respond to intravenous hypertonic solutions does not exclude its presence.

Summary

The importance of cerebral oedema in supratentorial tumours and active hydrocephalus in infra-

tentorial tumours causing slow activity in the E.E.G. is stressed.

Infiltrating supratentorial tumours may cause little mechanical distortion of normal cells and the E.E.G. may be normal. Actively expanding tumours cause marked slow activity.

The E.E.G. in subdural lesions was of little lateralizing value in this series.

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THE NOVEMBER (1954) ISSUE

The November (1954) issue contains the following papers :—

Focal Cerebral and Cerebellar Atrophy in a Human Subject Due to Organic Mercury Compounds. Donald Hunter and Dorothy S. Russell.

The Absorption and Excretion of Radiocopper in Hepato-lenticular Degeneration (Wilson's Disease). W. B. Matthews.

Adrenaline and Noradrenaline in Cerebrospinal Fluid. H. Weil-Malherbe and D. W. Liddell.

The Treatment of Manic Psychoses by the Administration of Lithium Salts. M. Schou, N. Juel-Nielsen, E. Strömgren, and H. Voldby.

The Sequelae and Short-term Prognosis of Attempted Suicide. The Results of a One-year Follow-up of 200 Cases. I. R. C. Batchelor and Margaret B. Napier.

The Effect of Temporal Lobectomy upon Two Cases of an Unusual Form of Mental Deficiency. D. W. Liddell and D. W. C. Northfield.

Pathological Findings in Temporal Lobe Epilepsy. Alfred Meyer, Murray A. Falconer, and Elisabeth Beck.

The Reticular Perivascular Tissue of the Central Nervous System. J. W. Millen and D. H. M. Woollam.

Case Report : Prenatal Occlusion of the Internal Carotid Artery. R. M. Clark and Eric A. Linell.

Case Report : Hairy Teratomatous Cyst in the Occipito-cerebellar Region. S. Obrador.

Periarteritic Lesions of the Carotid Siphon with the Clinical Features of a Carotid Infraclinoidal Aneurysm. Eduardo Tolosa.

Intramedullary Spinal Abscess. J. E. M. Dutton and G. L. Alexander.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 12s. 6d.

J. Neurol. Neurosurg. Psychiat., 1955, **18**, 72.

ALZHEIMER'S DISEASE WITH ACNE ROSACEA IN ONE OF IDENTICAL TWINS

BY

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Although Alzheimer's disease has been known for some 50 years it is only in the last 20 that any considerable literature has grown up around its genetic aspects. At a Royal Society of Medicine discussion on presenile dementia in 1932, for instance, Critchley could express legitimate surprise when two of the speakers cited familial cases of Alzheimer's disease and could point out with accuracy that no such familial cases had previously been reported in the literature. In that same year, however, Schottky (1932) described the occurrence of Alzheimer's disease in a father and daughter, and from then onwards sporadic cases of parent-child incidence and/or sibling incidence have continued to be reported. The most recent is that described by Essen-Möller (1946) and concerns a father, son, and daughter all of whom developed Alzheimer's disease in their fourth decade. Slater (1950), referring to this particular case, goes so far as to say that it gives support to " the prevailing impression that this disease depends on a dominant gene ", a statement which indicates the degree of acceptance of a genetic basis by some present-day writers on the subject.

The approach to the genetic aspects of Alzheimer's disease is often widened to include senile dementia. This attitude emphasizes that dichotomy of opinion on the nature of Alzheimer's disease which was not only apparent at its initial formulation but persists to the present day. Alzheimer (1907) regarded the syndrome described by himself as an atypical form of senile dementia, but Kraepelin (1910), impressed by the earlier age of onset and by a collection of symptoms which differed in his opinion from that found in senile dementia, was disposed to consider it a disease *sui generis*, for which he proposed the title of Alzheimer's disease. Those observers whose interest has been directed predominantly to the clinical aspects of Alzheimer's disease have continued to endorse Kraepelin's conclusion, holding that the early onset, the characteristic personality changes, the severe degree of intellectual deterioration with its profusion of focal symptoms of an aphasic and agnostic type, and the frequent coincidence of epileptiform seizures constitute a specific clinical entity distinct from senile dementia. Nevertheless, the underlying pathological changes are indistinguishable from those found in senile dementia. Consequently many authorities would deny the validity of any hypothesis which separates Alzheimer's disease from senile dementia. Newton (1948), in a study of the histopathological findings in 150 consecutive mental hospital necropsies, demonstrated miliary plaques in 14 of the 59 cases in the age group 60–64 years, and in 37 of the 52 in the age group 65–96 years, and concluded therefrom that Alzheimer's disease, senile dementia, and normal senility are " examples of the same condition occurring at different ages ". He considers that research into the aetiology of these conditions has failed to produce results because it has been sought in the environment and not in the cell itself : " the problem, therefore, becomes one of genetics ". The tacit acceptance of Newton's concept of the indivisibility of Alzheimer's disease and senile dementia is implicit in the work of Sjögren, Sjögren, and Lindgren (1952), who attempt the more specific task of establishing genetic uniformity between these two disease processes. Taking as their point of departure a group of 80 cases of presenile dementia admitted to various Swedish hospitals, they proceeded to investigate their families and forebears in considerable detail. The initial group was a somewhat heterogeneous collection consisting of 18 histopathologically verified cases of Alzheimer's disease ; 18 histopathologically verified cases of Pick's disease ; 29 cases with the generic title " Pick-Alzheimer syndrome " where cerebral atrophy had been verified by encephalography or post-mortem examination, but histopathological examination was lacking ; and 15 cases of Pick-Alzheimer syndrome where the diagnosis was based on clinical findings alone.

Investigation of the families of these 80 patients

revealed that in the family histories of 20 of them, 30 " secondary " cases were isolated. The diagnosis made in these " secondary " cases was that of senile dementia or Pick-Alzheimer syndrome. Sjögren and his colleagues consider these figures statistically significant. The inclusion in their material of cases of Pick's disease unfortunately confuses the issue. When attention is concentrated on the pedigrees of their 18 histopathologically verified cases of Alzheimer's disease we find that the first is the case of Essen-Möller (1946) referred to above and in only two others was there a history of senile dementia in one parent.

This recent preoccupation with genetic factors in Alzheimer's disease, whether or not extended to include senile dementia, makes it seem worth while to describe Alzheimer's disease in one of female identical twins. The other twin is still alive, aged 73, and is pursuing a normal life four years after the death of her sister, in whom symptoms first made their appearance at the age of 50.

Case Report

Mrs. Margaret O., aged 63, was admitted on March 5, 1943, to the Royal Edinburgh Hospital for Mental and Nervous Disorders, and died on October 12, 1949, being then 69 years of age.

The first deviations from normal occurred some 13 years before admission to hospital (in 1930, when the patient was aged 50), and took the form of gradually failing domestic efficiency associated with personality changes. Formerly meticulous about the weekly laundering, she now hung out articles inadequately washed. She became more irritable, less careful about her personal appearance, less interested in social outings. (The latter was first attributed to self-consciousness about an acne rosacea which made its appearance about this time.) She took a dislike to her twin sister, to whom she had been devoted. Over the ensuing 10 years there was a progressive but insidious deterioration of her mental faculties; she became slower in her performance of domestic duties and showed increasing memory defects. Three years before admission more florid mental symptoms of a delusional type appeared and ushered in a more accelerated decline. She accused her husband of consorting with other women, and on one occasion she locked the house against him, and on another attacked him with physical violence. Admitted for investigation to a general hospital, where her illness was diagnosed as cerebral arteriosclerosis, she accused the staff of immoral behaviour and attempted to escape through a balcony window. She had phases of nocturnal restlessness, when she would remove the black-out protection from the windows and disarrange the furniture. During the two years preceding her admission she was quite unable to attend to her household, and her memory defect was so extreme that she would turn on the gas and omit to light the jet. She became unable to carry on a conversation, having obvious difficulty in finding the necessary words, in forming sentences, and in retaining the gist of questions addressed to her. She could not write her name. She showed disorientation for time and place, misidentified persons in her environment (including her husband) and appeared to recognize only her two daughters. She took her food well and was not incontinent.

The patient was a healthy-looking middle-aged woman. A moderate degree of acne rosacea, characterized by erythema and acneiform papules and pustules, was present over the nose, cheeks, and left lower eyelid, but the conjunctiva was unaffected. Examination of the central nervous system revealed no focal neurological signs in the somatic sphere. Examination of other systems likewise showed no abnormality. A blood Wassermann reaction was negative.

When greeted, she responded by an immediate smile, and although obviously unable to achieve adequate verbal rapport, she indicated by gesture her eagerness to co-operate with the examiner. She showed a degree of psychomotor overactivity, constantly walking up and down the ward reiterating greetings to her fellow patients, and, during the interview, playing interminably with the cord of her dressing gown.

She proffered no spontaneous remarks but invariably responded to questions. Her replies, however, were usually incomplete and frequently inaccurate or irrelevant. She tended to grope for words, making one or two attempts before achieving accurate pronunciation. Her vocabulary was reduced to the simplest elements of speech, and her comprehension was so defective that she did not always understand questions couched in similarly simple terms. Asked her name, she replied, " Margaret (pause) eh, fancy now, that's funny, fancy I've forgotten. I've not been thinking. I was never like that. Just Margaret, isn't it ? " Asked her surname, she transposed components of her maiden and married names so that the resulting word sounded like an anagram of both. Asked her husband's name, she replied by giving his occupation, and on repetition of the question, perseverated by giving her own Christian name. Requests to demonstrate parts of her own body usually resulted in accurate responses. Shown simple objects she was able to evince some appreciation of their purpose : key, " putting in the door " ; matches, " for to light " ; letter, " I'll need my glasses ". She was unable to read sentences in large print, but on occasion pointed to random words and named them correctly. She was unable to write to dictation, to copy or to sign her own name. She could not essay the simplest calculations. Memory was grossly impaired. Given a name, a vegetable, and a colour, she was unable to repeat them after an interval of one minute. She could not recite any of the universally known jingles and nursery rhymes. Questions relating to previously acquired knowledge rarely obtained an accurate response, e.g., Q. " What is the King's name ? " A. " Isn't that funny, I should think (i.e., know) that " (with an air of bewilderment).

Her mood was euphoric : she smiled and laughed and was obviously unaware of her total situation. She seemed episodically surprised, however, by her inability to supply

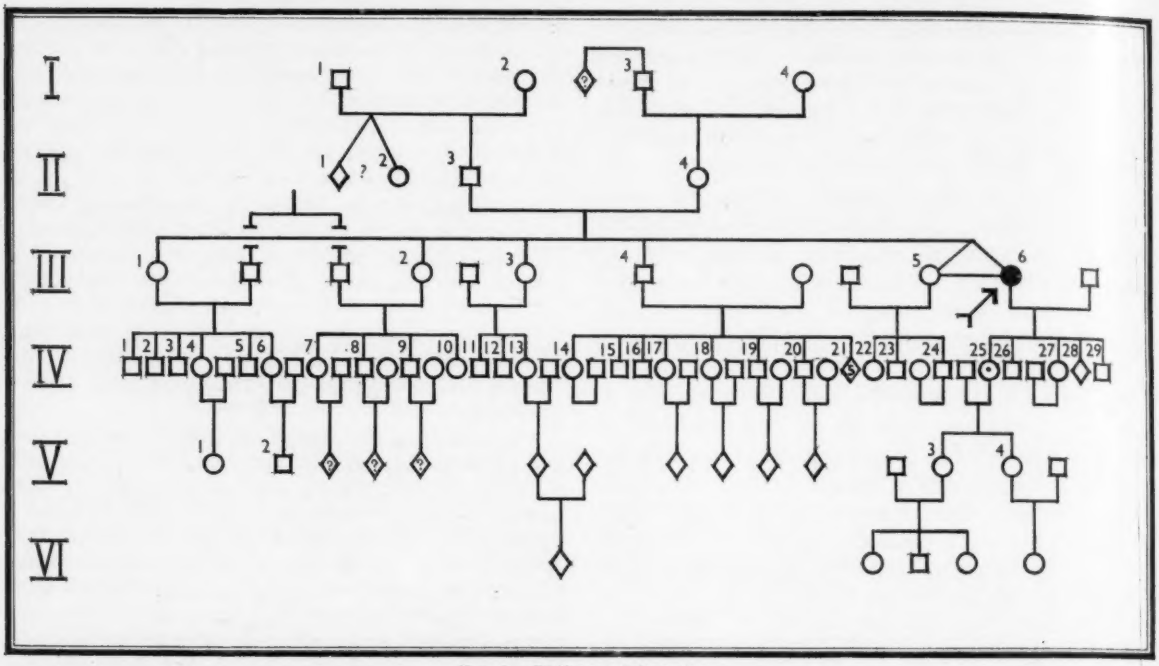

FIG. 1.—Pedigree of the twins.

I. 1 and 2, nothing known ; 3, died aged 45 years ; 4, died at 80 years.

II. 1 and 2, twins, uncertain if identical. 1, stillbirth ; 2, lived to old age ; 3, died at 62 years of silicosis ; 4, died at 62 years of gallstones.

III. 1 and 2 married brothers ; 1, died at 72 years of heart disease ; 2, died at 46 years of bronchitis ; 3, died at 30 years of inanition ; 4, died at 41 years of aortic disease and mitral incompetence ; 5, alive and well at 73 years, twin of 6 (propositus).

IV. 1–6 and 7–10, first cousins but genetically siblings ; 22–24 and 25–29, first cousins but genetically half-siblings. 1, died at 15 years of septicaemia ; 2, died at 49 years, cause not known ; 3, died in infancy ; 4, alive and well at 66 years ; 5, died at 50 years by accident ; 6, 7, 8, and 9, alive and well all aged 50 years ; 10, died at 14 years " faint at menarche " (*sic*) ; 11, 12, and 13, ? alive and well ; 14, died at 49 years, cause not known ; 15 and 16, died in infancy ; 17, 18, 19, and 20, alive and well ; 21, 5 others, nothing known ; 22, alive and well, acne of face, age 40 years ; 23, died at 1 year of diphtheria ; 24, alive and well, ? 35 years ; 25, died at 36 years, asthma following anaphylactic serum reaction at age of 25 years, had attacks of muscular rigidity with loss of consciousness, no mental disorder ; 26, died at 2 years of tuberculous enteritis ; 27, alive and well, ? 40 years ; 28, miscarriage.

V. 1, alive and well, 33 years ; 2, alive and well aged 29 years ; 3, alive, 20 years, in poor health following quick succession of pregnancies ; 4, 21 years, alive and well.

the demanded information, and her most sustained utterances took the form of artless rationalizations of her incapacity ; for example, " I let my man do everything. I see now I should have done things myself. He said ' Do it yourself .' I said ' You do it—you write nicer. ' "

Removed from hospital by her relatives after four months' residence, she was returned within 12 months because of the impossibility of caring for her at home. It was noted then that, while she still smiled brightly when addressed, questions and commands elicited no positive action or intelligible speech. Within two years of her return, her increasing unsteadiness of posture made it necessary to confine her to bed. During the last three years of her life she lay immobile, her head assuming the " psychical pillow " attitude mentioned by Critchley (1933), her limbs showing a hypertonus on passive manipulation. She also showed curious jerky movements of the trunk and limbs, which occurred at irregular intervals throughout the day. The latter were quite different in nature from the infrequent generalized epileptic fits which were also a feature of the terminal period. During her last year of life she became emaciated, developed contractures, and also recurring excoriation of the skin over dependent areas. Yet even at this stage she still essayed an answering smile when spoken to. The acne rosacea, present on admission, persisted unchanged till her death.

Investigation of the patient's ancestry, both direct and collateral, revealed no evidence of mental or nervous disease in any one member. There was no history of consanguineous marriages. The patient and her twin were born at the end of the reproductive life of the mother, who had had five previous pregnancies (Fig. 1).

History of Patient and Her Twin.—Margaret, our patient, and Chrissie, her twin, were born in 1880, and so far as is known no complications attended their birth, which occurred when their mother was 45 years of age. The patient was the second born of the twins. Both were breast fed. Their early development was similar. Their school records were comparable and somewhat above average. On leaving school, both went to work in the same paper factory and remained there till their respective marriages. They lived at home till the death of their parents and then lived together in the same lodgings. This close association ended in their twenty-seventh year

when Margaret married. Their paths diverged still further three years later when Chrissie left this country for her marriage in Australia. Margaret spent her entire life in her native town of Edinburgh. Chrissie lived for over 20 years in Australia, at first in Sydney and later in Brisbane. Following the death of her husband, she returned to Scotland with her two children in 1930. Met on her arrival by her twin, Chrissie was struck by something strange in Margaret's appearance and demeanour and always remembered her own first remark at that meeting, which was, "I hope *I* don't look like that". (It is significant that Chrissie was the first to notice the change in the patient's appearance and personality, although her husband had observed concomitantly the commencing failure in domestic efficiency.)

Each twin had two children who survived to adult life. Of Margaret's five pregnancies, the last two ended in miscarriages, and her second child died of tuberculosis in childhood. Chrissie had three full-term infants, the second of whom died in childhood of diphtheria.

FIG. 2.—The twins as young women.

Margaret (the patient) was regarded as being less robust than her twin in childhood, having frequently recurring sore throats and quinsy. Chrissie, however, suffered from both scarlet fever and whooping-cough, which her twin escaped. Margaret suffered from influenza during the 1918–19 epidemic, and the illness was severe with delirium and high fever. Chrissie, then in Australia, suffered from pleurisy the following year. Margaret had an attack of whooping-cough at the comparatively late age of 30.

All observers who knew them in youth were agreed that the twins resembled each other in personality traits as in appearance and mannerisms. Both were lively, high-spirited, and fond of playing practical jokes in which they impersonated each other, but conscientious at their work and regular in their church attendance. Minor temperamental differences existed. Margaret was more meticulous, more prone to worry and more sensitive than Chrissie. She was more easily moved to anger. She was less flexible, less adept at making friends, less adventurous in the world of business. Chrissie admitted frankly that her slightly greater social popularity arose from her "being more lazy and pleasant by nature".

Following the admission to hospital of the patient, Margaret, her twin, Chrissie, was examined by one of us (E. A. D.), who found that the twins showed all the similarities of physical configuration which are accepted as strong contributory evidence of uniovularity. Chrissie was so conscious of the close physical similarity existing between herself and her twin that she lived in constant dread of developing a similar illness, and since this feeling was exacerbated every time she saw her twin, she visited her in hospital at first infrequently and finally not at all. To this circumstance can be attributed the unfortunate

FIG. 3.—The twins after the onset of the patient's illness.

omission of finger-print and blood-group tests. All the available evidence, however, strongly confirmed uniovularity. The surpassing similarity of the twins was such that even members of their family circle were unable to distinguish the one from the other. The only person who could do so in childhood was their father, who, after keeping secret for many years his basis of identification, finally confessed that he was able to detect in Chrissie a slight droop of the left angle of the mouth not apparent in Margaret. Friends of one twin meeting the other in the street constantly greeted her as the twin of their acquaintance, and this misidentification was particularly marked on Chrissie's return from abroad, when she found

herself hailed as Margaret by all the latter's friends. A physical peculiarity confirming uniovularity was that when the hair of both twins turned white at the same time, at the age of 40, they each had a residual brown patch of hair in exactly the same position. Following Margaret's death, her daughter, when unexpectedly confronted by her aunt, was constrained to call out, " Oh, mother! "

A photograph of the twins taken in their youth reveals the striking similarity existing between them (Fig. 2). Another taken after the onset of Margaret's illness shows notable changes in her appearance, in the form of flattening of the facial muscles, a certain fixity of expression, and a sloppiness and lack of fashion in her dress (Fig. 3).

In an interview, following the patient's admission to hospital, her twin, Chrissie, gave a clear and concise account of the patient's early history and the various stages of her illness. Chrissie had no difficulty in word finding, in recalling recent and remote events, or in describing minutiae of temperamental similarities and differences existing between the patient and herself. Although willing to proffer information, she refused to submit to formal intelligence tests. The examiner however was able to conclude from her alert attitude and intelligent conversation that she showed no evidence of the cerebral disease which afflicted her twin.

She was interviewed 10 years later (July, 1953) by the same examiner (E. A. D.) who had seen her on that earlier occasion. Chrissie, then aged 73, was an alert and active housewife, who dealt efficiently with the cooking, domestic cleaning, and shopping required in a household consisting of herself and a daughter who went out to business each day. Her physical appearance vividly recalled that of the patient at the age of 63, allowing for such important differences as her neater style of dress and absence of facial rash. The ease with which she supplied chronological data to amplify the family history showed that she had no memory disorder. She answered all factual questions quickly and relevantly, although she was still somewhat hesitant in speaking about her sister's illness, a hesitancy which was interpreted as indicating some still persisting anxiety on this subject. In neither speech nor action did she give any impression of intellectual deterioration, and her excellent physical and mental health was confirmed not merely by her daughter, but by the more impartial evidence of neighbours and friends.

Necropsy Report

The body was that of an extraordinarily emaciated elderly woman with sacral bedsores. Permission was granted to examine only the brain, which showed gross generalized atrophy.

Brain after Fixation.—The leptomeninges had a cloudy opalescent appearance. The basal vessels showed patchy atheroma. Marked gyral atrophy with widening of the sulci was apparent over both cerebral hemispheres, the atrophy being particularly severe in both frontal lobes and adjoining anterior parts of both parietal lobes. A serial coronal section of the cerebrum revealed distinct atrophy of both grey and white matter with compensatory dilatation of the ventricles.

Histology.—Sections were examined from the frontal, parietal, and occipital lobes, cornu Ammonis, basal ganglia, and midbrain. Chromatin stains and metallic impregnation methods were used. The small meningeal and cerebral vessels revealed no pathological change. All parts of the cortex showed widespread loss of nerve cells from all layers, while many surviving cells were shrunken and atrophic, often showing senile lipochrome pigmentation. There was a considerable proliferation of coarse fibrillary astrocytes in all parts of the grey matter. In addition, numerous well formed argyrophile plaques were present throughout the cortex, while some of the surviving nerve cells showed thickening of their intracellular neurofibrils, producing Alzheimer's neurofibrillary tangles, although this last feature was not quite so marked here as in many cases of Alzheimer's disease.

Discussion

If the twins are accepted as being monozygotic, environmental aetiological factors may be said to be proved in this instance of Alzheimer's disease, the significant factors being obscured by the multiple deviations found in comparing the two life histories. Of the divergent aspects of the histories, special mention may be made of the febrile delirium from which the affected twin suffered during the 1918–19 influenza epidemic, since this illness may have been encephalitis. Greenfield and Bosanquet (1953) have found neurofibrillary tangles similar to those found in Alzheimer's disease in the pigmented cells of the brain-stem in post-encephalitic Parkinsonism, and quote other authors who have described similar changes in the cortical nerve cells in cases of subacute inclusion and subacute sclerosing encephalitis. Also of possible significance is the 20 years' residence of the unaffected twin in Australia, with its different climatic and dietary conditions and its relative freedom from dietary restriction during the 1914–18 war.

Genetic aetiological factors in Alzheimer's disease, demonstrated by various authors, can be neither proved nor disproved in our case. Patterns of inheritance strongly suggestive of the transmission of a recessive gene are found in the pedigrees of Alzheimer's disease described by Lowenberg and Waggoner (1934) and by McMenemey, Worster-Drought, Flind, and Williams (1939). Those first affected were the children of first-cousin marriages: the appearance of the character in the subsequent generation in each pedigree can be explained only by the mating of a homozygous affected with a heterozygous normal, a circumstance indicative of a relatively high rate of heterozygous normals in the population. The family histories of cases described by Schottky (1932), Grünthal and Wenger (1939), van Bogaert, Maere, and de Smedt (1940), who described two cases, and Essen-Möller (1946) all

admit of transmission of an autosomal or partially sex-linked dominant gene, there being in each instance a "vertical" distribution of affected persons, of whom all had one affected parent so far as could be traced.

From the available evidence, we must either ascribe to this clinico-pathological entity alternative aetiological factors of such diversity as heredity and environment or agree with McMenemey (1940) that "both endogenous and exogenous factors may be involved in any given case with pathology of the Alzheimer type". It may be that, in the ostensibly hereditary cases, environmental factors determine the timing and degree of expression of genetic factors.

An interesting feature of this case was the acne rosacea which appeared simultaneously with the mental symptoms and was never present in the healthy twin. Lewis (1934) has reported discordance for acne rosacea and acromegaly in uniovular twins, whereas Hutchinson (1891) and Lesser (quoted by Siemens, 1926) describe hereditary cases of rosacea. The discordance of monozygotic twins for two genetic characters would favour the possibility of somatic mutation having occurred in one twin. In such a circumstance a gene with pleiotropic effects must be envisaged or disturbance of the gene company by mutation allowing for the expression of a linked gene. Such mutation occurring in one of identical genotypes must be determined by environmental factors.

We have recently observed the association of Alzheimer's disease with rosacea in a second case. A third case of Alzheimer's disease, an emaciated patient, showed widespread bu lous eruptions and skin atrophy which, together with the cerebral lesion, were confirmed at necropsy. These cases are of interest, since Schottky (1932) believed that hereditary impairment of the primitive ectoderm was probably a factor in Alzheimer's disease. The validity of this theory could be tested by clinical scrutiny of the ectodermal structures and skin biopsy in early cases.

Summary

Monozygotic twins discordant for Alzheimer's disease and acne rosacea are described. Neuropathological findings in the affected twin are reported.

Environmental factors are, of necessity, postulated to account for the discordance.

The significance of the findings is discussed in relation to aetiological factors in Alzheimer's disease.

We wish to express our thanks to Professor Sir David K. Henderson for permission to publish this case and to Professor F. A. E. Crew for his advice on the genetic aspects. We are indebted to Dr. W. M. McAlister for permission to study skin biopsies at Bangour Mental Hospital and to Dr. N. Maclean for the histological report on a section of skin. Miss R. Morrison, psychiatric social worker, gave invaluable assistance in tracing the family history.

The neuropathological examination of this case of Alzheimer's disease was carried out by the late Dr. William Forbes.

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CORRECTION

In the paper on "The Effect of Temporal Lobectomy upon Two Cases of an Unusual Form of Mental Deficiency", by D. W. Liddell and D. W. C. Northfield, in the November, 1954, issue, the E.E.G. in Fig. 6, page 270, should be transposed with that in Fig. 7, page 272.

BOOK REVIEWS

The Epileptic Cramp Attack as a Psychosomatic Reaction. By Raf Gordin. (Pp. 167. Dan. kr. 20.–.) Copenhagen : Ejnar Munksgaard. 1953.

This small book considers in detail the case histories of 22 patients with epilepsy. The medical biographies of the cases are taken on broadly psychoanalytic lines with emphasis on emotional factors, analysis of dreams, and personality traits shown in reaction to the general stresses and demands of life, though it seems unlikely that the author is himself an accredited psychoanalyst. The cases are supposed to support the argument that epilepsy is a psychosomatic disease in the sense of a somatic reaction to psychological causative factors. Treatment on psychological lines, which is never mentioned in any detail, produced some improvement in most cases and marked improvement in a few. This is taken to support the author's thesis. However, the natural variability of epilepsy casts doubt on this latter argument, while case histories similar to those he quotes must be familiar to all psychiatrists in patients who do not have epilepsy, which weakens their evidential value for the psychosomatic nature of epilepsy. That psychological factors must play some part in the occasion of an epileptic fit is a logical necessity once dysfunction of thalamus and cortex is admitted as a background to epilepsy. This book, however, adds nothing of value to this very important aspect of the problem. On the contrary, it may be a stumbling block to progress, for it is written in a kind of pidgin English, bizarre and misleading, and sometimes ludicrous, and may thus encourage those reading it to dismiss, mistakenly, the whole question of psychogenic factors in epilepsy as part of the " lunatic fringe " of medicine.

Clinical Psychiatry for Practitioners and Students. By Ian Skottowe. (Pp. 375. 36*s*.) London : Eyre & Spottiswoode. 1953.

The choice before the writer of a psychiatric textbook is hard : he must either tread in the respectable footsteps of his forerunners or run a little wild. Dr. Skottowe has elected for the former, and although his book is up to date and well organized it follows assured middle-of-the-road lines which are fairly familiar. Admirable advice is given ; extensive use is made of the author's wide clinical experience, and the inexpert reader is not puzzled by obscure psychopathological excursions or pelted with references to specialized literature. The practitioners and students for whom the book is meant can depend upon it for a trustworthy and practically helpful picture of commonsense psychiatry ; but they must not expect critical sallies or lively reviews of the pros and cons of unsettled procedures such as group psychotherapy, carbon dioxide inhalations, or projective tests of personality. The book is, in short, safe and sound.

Integration Linearer Kutaner Schmerzreize (Integration of Linear Cutaneous Pain Stimuli). By Alf Breig. (Pp. 65 ; 39 figures. DM. 7.20.) Stuttgart : Georg Thieme Verlag. 1953.

This monograph is difficult to render into English which is easily comprehensible. Nevertheless, the author has made certain observations which will be of interest to clinical neurologists. Briefly, he has demonstrated that if a sharp object like a needle is dragged quickly, lightly, and evenly across the skin in any region of the body the subject will report an unequivocal sensation of pain only after the needle has traversed a given distance. For a given pressure the distance travelled before the onset of pain is proportional to the velocity of the point. The pressure used is not an important variable ; it is only necessary that the point should be clearly felt and arouse no pain when dragged slowly across the skin. The author concludes that these observations are evidence of spatial and temporal " summation " of pain impulses, and in so far as pain aroused by radiant heat can be compared with pain aroused by mechanical means his observations are at variance with those of Hardy, Wolff, and Goodell.* The author demonstrates the importance of his observations in clinical neurology by indicating that the mapping out of dermatomes in cases exhibiting cutaneous hyperalgesia is often quite artificial owing to the failure of observers to take this effect of " summation " of pain impulses into account. He shows that any number of " pain " contour lines can be demonstrated in normal subjects depending upon the position on the skin at which the stimulus starts. When a number of such lines are mapped they are found to correspond to the contours of the body. He believes that hyperaesthetic zones in root and such-like nerve lesions are usually artificial and dependent upon the preconceived notion of the examiner when demonstrated in this way. He pleads that a succession of pinpricks also gives false information of a similar kind. He cites in support of his claims much neurohistological and physiological evidence for the view that a sharp border between adjacent nerve roots is unlikely.

*Hardy, J. D., Wolff, H. G., and Goodell, H. (1952). *Pain Sensations and Reactions.* The Williams and Wilkins Company, Baltimore.